



UNIVERSITY OF
LIVERPOOL

Efficacy and safety of paediatric immunization-linked intermittent preventive treatment in infants (IPTi) in the prevention of malaria morbidity in rural western Kenya.

Thesis submitted in accordance with the requirements of
the University of Liverpool for the degree of Doctor in
Philosophy

by

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July 2008

Liverpool School of Tropical Medicine

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Abstract

Efficacy and safety of paediatric immunization-linked intermittent preventive treatment in infants (IPTi) in the prevention of malaria morbidity in rural western Kenya

Frank Ouma Odhiambo

Background: Intermittent preventive treatment in infants (IPTi) with sulphadoxine-pyrimethamine (SP) for the prevention of malaria has shown encouraging results in recent trials. However, resistance to SP is rising and alternative drugs for IPTi need to be evaluated.

Objectives: To evaluate the safety and efficacy of different drugs for IPTi and to better understand the role of treatment vs. prophylactic effect of IPTi by comparing short and long-acting antimalarials.

Methods: In an area of western Kenya with stable perennial malaria transmission and high usage of insecticide-treated nets, we conducted a randomized, double-blind, placebo-controlled trial with SP plus 3 days of artesunate [SP-AS3], 3 days of amodiaquine-artesunate [AQ3-AS3], or 3 days of chlorproguanil-dapsone [CD3] administered at routine expanded programme of immunization visits (10 weeks, 14 weeks and 9 months). The primary endpoint was time to first or only episode of clinical malaria in the first year of life. Data was analysed using regression and survival analysis in SAS and STATA. The ClinicalTrials.gov identifier was NCT00111163.

Results: 1365 children received ≥ 1 dose of study drug and were included in the ITT analysis. The incidence of clinical malaria during the first year of life was 0.98 per PYAR in the placebo group and the median time to first episode was 196 days, compared to 204 ($p=0.01$), 208 ($p=0.007$) and 196 ($p=0.633$) in the SP-AS3, AQ3-AS3, and CD3 group, respectively. The corresponding protective efficacies (PE) and 95% confidence intervals (CI) against clinical malaria were: PE 25.7% (6.3, 41.1); 25.9% (6.8, 41.0); and 16.3% (-5.2, 33.5) for SP-AS3, AQ3-AS3, and CD3 respectively. When multiple episodes of clinical malaria were considered the corresponding results were 22.2% (95% CI: 2.5, 37.8; $p=0.029$), 24.7% (95% CI: 6.4, 39.5; $p=0.011$), and 10.5% (95% CI: -11.6, 28.2; $p=0.324$). A more specific case definition for clinical malaria (with >5000 par/ μ L of blood) showed much higher PEs; 48.9% (95% CI: 12.2, 70.3; $p=0.015$), 41.2% (95% CI: 2.5, 64.5; $p=0.04$), and 3.4% (95% CI: -52.3, 38.8; $p=0.88$). The PEs against the first or only episode of mild anaemia (Hb <11.0 g/dL) was 16.4% (95% CI: -0.6, 30.4; $p=0.057$) in the SP-AS3 arm, 20.3% (95% CI: 4.0, 33.9; $p=0.017$) in the AQ3-AS3 arm, and 8.0% (95% CI: -10.6, 23.5; $p=0.375$) in the CD3 arm. The corresponding figures for moderate-to-severe anaemia (Hb <8.0 g/dL) were 27.5% (-6.9, 50.8), 23.1% (-11.9, 47.2), and 11.4% (-28.6, 39.0) for SP-AS3, AQ3-AS3, and CD3 respectively. None of the regimens appeared to provide statistically significant protection against, all-cause out-patient visits, all-cause hospitalizations, malaria-related hospitalizations, or hospitalizations related to moderate-to-severe anaemia. A very high protective efficacy was found against the first or only episode of clinical malaria within a period of 30 days after the first course of IPTi. Post-dose analyses suggested a significant protective effect for at least 4 weeks with SP-AS3 and AQ-AS3, and at least 2 weeks for CD3. Importantly, there was no evidence of a sustained effect of IPTi after this initial period for any of the three drug combinations. There was no evidence for a consistent rebound effect in the second year of life. All regimens were well tolerated. Out of a total of 11,568 drug doses administered, only 2.1% were vomited. The total rate of vomiting across the 3 courses was significantly higher with each drug intervention than with placebo. There were 593 serious adverse events (SAEs) recorded during the 1st year of life. Of these, 55 were deaths, and 538 were hospitalizations. There was no significant difference in the number of SAEs recorded between the treatment and the placebo arms. There were no cases of severe haemolysis recorded. Further analysis showed that being a G6PD deficient male in the CD3 arm significantly increased ones' chances of having moderate-to-severe anaemia in the first year of life, -166.8% (95% CI: -497.5, -19.1; $p=0.017$). Serologic responses to EPI vaccines are pending.

Conclusion: The results suggest that long-acting regimens are more suitable for IPTi than short-acting regimens in areas with high ITN usage and perennial malaria transmission, and the evidence suggests that the post-treatment prophylactic effect of the long-acting regimens provide an important component of the protective effect of IPTi, and appears to last as long as the direct pharmacological effect of the drug. There was no evidence for a sustained beneficial or harmful effect beyond this immediate period of protection.

Dedication

To the memory of my late sister Ms. Winifred Akinyi Olulo, may she rest in eternal peace.

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Abbreviations used in the text

ACT	Artemisinin based combination therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANC	Antenatal clinic
AS	artesunate
AQ	amodiaquine
AQ3-AS3	Amodiaquine+artesunate for 3 days
BASF	Baden Aniline and Soda Factory
BMGF	Bill and Melinda Gates Foundation
CD	Chlorproguanil-dapsone
CD3	Chlorproguanil-dapsone for 3 days
CDC	Centers for Disease Control and Prevention
DDT	dichlorodiphenyltrichloroethane
DHFR	dihydrofolate reductase
DHPS	dehydropteroate synthetase
dL	deci-litre
DSMB	Data Safety and Monitoring Board
DSS	Demographic Surveillance System
EDTA	Ethylene diamine tetra acetic-acid
ELISA	Enzyme linked immunosorbent assay
EPI	Expanded programme of immunisation
GCP	Good Clinical Practice
G6PD	Glucose-6-phosphate dehydrogenase
GMT	Geometric mean titre
Hb	Haemoglobin

List of abbreviations

HCH	Hexachlorohexane
HIV	Human Immuno-deficiency virus
ERC/IRB	Ethical Review Committee/ Institutional Review Board
IPTi	Intermittent Preventive Treatment or Therapy in infancy
IPTp	Intermittent Preventive Treatment or Therapy in pregnancy
IRS	Indoor residual spraying
ITN	Insecticide treated net
ITT	Intention to treat
KEMRI	Kenya Medical Research Institute
LLITN	Long lasting insecticide treated net
LSTM	Liverpool School of Tropical Medicine
MDA	Mass drug administration
mg	Milligrams
PCR	Polymerase Chain Reaction
PE	Protective efficacy
PK	Pharmacokinetic
pLDH	Parasite lactate dehydrogenase
PPT	Per-protocol
PYAR	Person years at risk
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SAE	Serious Adverse Event
SJS	Stephen Johnson syndrome
SD	Standard deviation
SOP	Standard operating procedure
SP	Sulphadoxine-pyrimethamine
SP-AS3	1 course of sulphadoxine-pyrimethamine and artesunate for 3

List of abbreviations

	days
T _{1/2}	plasma half-life
TPP	Target product profile
UNICEF	United Nations Children’s Fund
WHO	World Health Organisation
WHOPES	World Health Organisation Pesticide Evaluation Scheme

Acknowledgements

I am extremely grateful to all participants, their parents and the entire community in Asembo. Without their collaboration this trial would not have been possible.

Very special thanks go to Dr. Robert Newman, who originally initiated and developed the concept of this study, for graciously allowing me to use the trial for my PhD studies.

I would like to extend my thanks to my supervisors in Kenya Dr. John Vulule and Dr. Mary Hamel for their continued support and assistance on site. I would also like to thank my PhD advisors Professor Bernard Brabin and Dr. Imelda Bates for their support and encouragement. I am very grateful to Dr. Larry Slutsker, Dr. Kimberly Lindblade, Dr. John Williamson and Ms Elizabeth Peterson for their invaluable support.

My heartfelt gratitude goes to my supervisors Professor Feiko ter Kuile and Dr. Dianne (Anja) Terlouw for their constant support, encouragement, advice and guidance given throughout the course of my studies, the preparation and writing of this thesis.

My sincere thanks go to the Kisumu IPTi team and all my colleagues at the CDC/KEMRI programme in Kisumu, who were directly and indirectly involved in the IPTi trial and to the Director Dr. Kayla Laserson for making it possible to complete the study.

Acknowledgements

I am deeply indebted to my dear wife Jolanta and children Pavel, Joanna and David for their patience, kind understanding and unwavering support that made it possible for me to dedicate four years of my life to conduct this trial.

I am greatly indebted to the IPTi Consortium and the Centers for Disease Control and Prevention in Atlanta, through which the IPTi trial was funded by the Bill and Melinda Gates Foundation, and the technical support provided by the following:

- DAFRA pharmaceuticals, especially Dr. Herwig Janssen
- The trial monitors Ms. Cornelia Bevilacqua and Dr. Alfred Tiono
- The Data Safety Monitoring Board (Dr. Bill Watkins, Dr. Jim Todd, Dr. Juliana Otieno, Dr. James Dinulos)
- The Consortium Safety Panel (Sir Alasdair Breckenridge, Dr. Julia Critchley, Dr. Alex Dodoo, Dr. Zul Premji, Dr. Esperanza Sevene, Dr. Rachida Soulaymani, Professor Peter Winstanley)
- The Kenya Medical Research Institute

The Liverpool School of Tropical Medicine, especially the Child and Reproductive Health Group

Statement of involvement of the PhD candidate in the IPTi trial

The IPTi trial based in Kisumu was conducted in rural western Kenya in an area adjacent to Lake Victoria, from March 2004 to March 2008. It is one of the four trials conducted by the IPTi Consortium funded by the Bill and Melinda Gates Foundation (BMGF).

Dr. Robert Newman and Dr. Laurence Slutsker were responsible for study rationale and design. Ms. Elizabeth Peterson, Mr. Peter Otieno, Dr. Kimberly Lindblade and the PhD candidate were responsible for the set-up of the field sites and standard operating procedures. Mr. Peter Otieno was responsible for day-to-day supervision of field staff and Dr. Simon Kariuki and Mr. Philip Onyona were responsible for the Laboratory work. The PhD candidate and Dr. Mary Hamel had overall responsibility for the conduct of the trial. The PhD candidate was directly responsible for coordination of all field activities and laboratory activities; data management; trial documentation in accordance with GCP guidelines; interaction and correspondence with trial monitors; compilation of regular reports to the DSMB and CSP; annual reports to KEMRI, CDC, and the IPTi Consortium; and management of study personnel, budgeting and procurement of supplies. The PhD candidate and Ms. Evallyne Sikuku were responsible for data cleaning, data analysis and reporting. The analysis plan was prepared by the PhD candidate in consultation with Dr. Robert Newman, Professor Feiko ter Kuile, Dr. Laurence Slutsker and the IPTi Consortium. The data

Statement of involvement of the PhD candidate in the IPTi trial

analysis was led by the PhD candidate with input from statistician Dr. John Williamson, Professor Feiko ter Kuile, and Dr. Robert Newman.

The preparation and writing up of this thesis was done by the PhD candidate with support and guidance from the PhD supervisors Professor Feiko ter Kuile and Dr. Dianne (Anja) Terlouw.

Chapter 1: Preface

Introduction

In the late 1990s, the resurgence of malaria across sub-Saharan Africa led to the formation of the Roll Back Malaria partnership that set goals to halve the burden of malaria worldwide by the year 2010 and halve that again by 2015, using techniques that already existed or which could be rapidly developed (WHO, 1998). A major political turning point for sub-Saharan Africa was realised during the summit held in Abuja, Nigeria in 2000 where African leaders adopted the Abuja declaration committing their respective governments to achieve set goals in malaria control and prevention (WHO/CDS/RBM, 2002). Since that summit, there has been an increased emphasis on malaria prevention through various strategies, including intermittent preventive treatment in pregnant women (WHO, 2004b).

Intermittent preventive treatment is a strategy, which aims to gain most or all of the benefits of chemoprophylaxis, while avoiding its main drawbacks. Intermittent preventive treatment can be defined as drug administration, in curative doses, given at regular intervals to asymptomatic individuals already attending facility-based care (for example ante-natal visits), with the objective of preventing malaria. Drugs are provided irrespective of the presence of parasites or symptoms. The main difference from chemoprophylaxis is the fact that in the latter, anti-malarial drugs are given

regularly at sub-therapeutic doses with the objective of sustaining a protective drug level that inhibits the development of the malaria parasite.

The strategy mentioned above has been broadened to include infants and a number of trials have demonstrated the benefits of intermittent preventive treatment in infants (IPTi) with sulphadoxine-pyrimethamine when given at the same time as childhood vaccinations (Schellenberg et al., 2002, Chandramohan et al., 2005, Macete et al., 2006, Kobbe et al., 2007, Grobusch et al., 2007b, Mockenhaupt et al., 2007)

The study described in this thesis was designed to further investigate alternative drug candidates to sulphadoxine-pyrimethamine and issues regarding the mode of action of IPTi which is a promising tool for malaria control and has the potential to boost the efforts to avert the senseless loss of life attributed to malaria.

Outline of the thesis

This thesis consists of the following seven chapters:

- Chapter 1 introduces the thesis.
- Chapter 2 reviews literature that is relevant to IPTi. The first section describes the burden of malaria morbidity in children, the second section gives a brief assessment of malaria control strategies, and the third section provides a more detailed account of the concept and rationale of IPTi, completed studies, the current body of

evidence available, and the implications for its future as a malaria control strategy.

- Chapter 3 describes the country and site of study, with the first section giving a brief outlook of the country, and the second section providing more details about the study site and available research facilities.
- Chapter 4 gives an outline of the materials and methods used including a brief mention of study procedures and a comment on the rationale behind the choice of investigational drugs.
- Chapter 5 presents the results illustrated with figures and tables.
- Chapter 6 discusses the results within the context of the current body of knowledge and touches on relevant contemporary issues.
- Chapter 7 provides conclusions and recommendations based on the findings of this study.

Chapter 2: Literature review

The burden of malaria morbidity

The burden of malaria in children

The global burden of malaria is estimated at over 500 million episodes of clinical malaria per year (Snow et al., 2005) resulting in a potentially preventable death toll of between 700,000 and 2.7 million deaths of children < 5 years of age each year, with sub-Saharan Africa contributing over 89% (WHO and UNICEF, 2005, Breman, 2001).

In 2002, it was estimated that over 800,000 deaths occurred among children <5 years of age in sub-Saharan Africa where malaria and anaemia are two of the leading causes of paediatric hospital admissions and acute febrile illnesses are responsible for 400 to 900 million hospitalizations per year (Breman et al., 2001, Slutsker et al., 1994, WHO and UNICEF, 2005).

In such hard-hit regions, repeated malaria episodes may impair a child's physical and cognitive development and reduce the child's attendance and performance at school (Bloland et al., 1999, Holding et al., 1999, Brooker et al., 2008, Clarke et al., 2008).

There is scanty information about the cost of malaria and the cost-effectiveness of different preventive measures but estimates suggest that Africa regularly sustains economic losses amounting to approximately US\$12 billion per year and the disease may slow economic growth by 1.3

percent per year as a result of lost life and lower productivity (Gallup and Sachs, 2001, Sachs and Malaney, 2002). Malaria thus contributes to poverty, which in turn exacerbates the disease burden, trapping many endemic communities in a vicious cycle of suffering from illness and poverty (Sachs and Malaney, 2002).

The burden of anaemia in children

Anaemia affects approximately one-quarter of the world's population and is concentrated in preschool-aged children and women. The most recent estimated global anaemia prevalence is 47.4 % in preschool-aged children, affecting 293 million children (McLean et al., 2008). Recent estimates for Africa are lacking but approximately three quarters of preschool children in eastern Africa suffer from anaemia, defined as haemoglobin (Hb) concentration below 11 g/dL (Arantxa Roca-Feltrer, 2008).

Anaemia in early childhood leads to impaired physical growth and mental development, decreased physical fitness and resistance to infections (Lozoff et al., 1987, Lozoff et al., 1991, Idjradinata and Pollitt, 1993, Lawless et al., 1994, Chwang et al., 1988), increased risk of subsequent obstetric complications in girls (Gillespie et al., 1991, Brabin et al., 2003) and, when blood transfusions are needed, increased risk of HIV infection and other blood-borne pathogens (Kerouedan et al., 1994).

Iron deficiency and malaria have been regarded as the predominant causes of anaemia among African children. Their relative contribution depends on age, season and geographical area, reflecting local and time-dependent

patterns in the availability of iron-containing foods and malaria transmission. Children are at highest risk for either iron deficiency anaemia or malarial anaemia between 6 and 36 months of age. In preschool children, iron deficiency predominantly results from a poor dietary intake of iron coupled with rapid body growth. For African children < 5 years of age, the overall incidence of severe malarial anaemia (Hb < 5 g/dl) is estimated at 15-60 cases per 1,000 children per year (Murphy and Breman, 2001). Although hookworm and schistosomiasis may be contributory factors in children in this age range, during infancy the prevalence and intensity of these infections is typically low. For example in western Kenya only 4.0% of infants were infected with hookworm and <1% with *Schistosoma mansoni* (Desai et al., 2005). Nevertheless, severe anaemia due to severe hookworm infections has been described even in very young children (Nkhoma et al., 2005).

Malaria-associated severe anaemia is an important cause of hospital admissions in malaria-endemic areas (Calis et al., 2008). In one hospital in Malawi, nearly 10% of admissions were for malaria-related severe anaemia; the peak prevalence occurred among infants aged 6-11 months (15%) (Slutsker et al., 1994). These rates were lower in children admitted to a hospital in an area not holo-endemic for malaria (Slutsker et al., 1994). Other studies have confirmed that the burden of malaria-related anaemia in areas with intense malaria transmission falls primarily on infants and young children (Shiff et al., 1996, McElroy et al., 1999).

Although it is well known that malaria is associated with anaemia, the dynamics in infants is not well known. Most falciparum infections in infants, especially in young infants, are of low density and remain asymptomatic (i.e. are not associated with fever). In Kitua's study in Tanzania, it was shown that the youngest infants up to 7 months of age are more sensitive to the impact of these low density infections on reducing levels of Hb than older infants; by the age of 12 months infants with low density infections had similar Hb levels to uninfected children (Kitua et al., 1997).

These data suggest that malaria related anaemia is an enormous public health problem in sub-Saharan Africa, that infants bear the greatest burden of the disease, and that because anaemia is often associated with asymptomatic malaria infection, prevention rather than treatment strategies are essential for combating the problem.

The global malaria control programme

Over the years, vector control has been and still remains the most generally effective measure to prevent malaria transmission. Initially, intensive control measures targeting larval control like sanitation and environmental modification were rigorously applied with great success in the well organised, highly urbanised and economically well endowed areas (Curtis, 1996). In many tropical areas and especially sub-Saharan Africa, such control programmes were not feasible, so early diagnosis and prompt treatment using chloroquine was the mainstay for malaria control until recently (Curtis, 1996).

The discovery of dichloro-diphenyl-trichloroethane (DDT) brought with it a formidable weapon that could be used to interrupt malaria transmission. DDT's residual effect against adult stage mosquitoes resting on walls indoors, which required only one or two treatments per year, made it operationally feasible to extend vector control to cover extensive rural areas. Spectacular achievements were reported from southern Europe, North America and Taiwan among other countries, and so the malaria eradication campaign was launched in 1955 with indoor residual spraying (IRS) using DDT and later with other residual insecticides. By early 1970s, malaria had been eliminated from Europe, most of North America, the Near East, most of the Caribbean, Australia and some countries in the Far East (Bruce-Chwatt, 1980).

The African experience during the “Malaria Eradication Era”

The “eradication of malaria” was never formally recommended for the African continent (WHO, 1969), and the Malaria Conference in Equatorial Africa convened by WHO in 1950 in Kampala (Uganda) was probably the first coordinated attempt to find a strategy for malaria control in Africa guided by WHO (WHO, 1951). The “malaria eradication era” in Africa translated into applied field research activities in a large number of studies across the continent. The initial studies between 1950 and 1964 mainly involved the use of DDT and hexachlorohexane (HCH) for residual insecticide spraying, and targeted chemoprophylaxis in some programmes (WHO, 1984). Of all the studies, actual interruption of malaria transmission

was only reported in 3 relatively small projects, two of them in forested areas of Liberia and Cameroon, and one in the western highlands of Uganda. In holoendemic areas, the most important projects that were conducted at the time were probably the Taveta-Pare Malaria Scheme (Wilson, 1960), in the savannah area adjoining Kenya and Tanzania, and the Western Sokoto Malaria Control Pilot project in northern Nigeria (Bruce-Chwatt, 1958). These projects demonstrated that malaria transmission could be considerably reduced and recorded dramatic reductions in the population of *An. funestus* (Gillies, 1977). However, by 1959 when WHO convened the Technical Meeting on Malaria Eradication in Africa in Brazzaville (Congo), it had become apparent that major financial, administrative and technical difficulties would have to be overcome in order to “eradicate malaria” in Africa (WHO, 1967). The studies carried out in the subsequent period between 1965 and 1974, recognized that any prospect of “eradicating malaria” were strongly associated with access to basic health services which was largely lacking in most countries. This led to the concept of pre-eradication programmes which attempted to develop basic health services concurrently with early eradication programmes.

Unfortunately, the implementation of pre-eradication programmes turned out to be impracticable (WHO, 1967), and more realistic strategies were sought at the 22nd World Health Assembly (WHO, 1969). Evidence of the development of resistance to pesticides like DDT and drugs like chloroquine, and well documented studies like the Garki project in Sudan showed that there was no single affordable method that could be used to interrupt malaria transmission across the entire African continent

(Molineaux, 1980). Therefore, different regions would have to adopt different strategies for malaria control. It also became clear, that it may not be possible to “eradicate malaria” in certain areas in Africa (WHO, 1974), given the conditions of ordinary life in rural areas, mobility of the population, lack of appropriate health services infrastructure, severely limited financial resources coupled with the tropical climate and environmental conditions that proved highly conducive for the survival of the vector. Furthermore, these tropical and sub-tropical areas had an abundant population of highly efficient vectors like *Anopheles gambiae* and *Anopheles funestus* with an estimated vectorial capacity >60%, which favoured stable malaria transmission in some areas and very high seasonal transmission in other areas (Snow, 2002). The emergence of resistance to DDT and the banning of its use in agriculture led to the abandonment of spraying in favour of case treatment. Indeed, the threat of malaria was greatly reduced worldwide as a result of the widespread use of chloroquine for treatment and chemoprophylaxis.

Re-emergence of Malaria in Africa

In the late 1990s, there was a strong resurgence of malaria in sub-Saharan Africa, resulting primarily from increasing rates of treatment failure to chloroquine due to a rapid rise in resistance caused by its indiscriminate and uncontrolled use for malaria control. In response to the worsening situation, a Ministerial Conference was convened in Amsterdam in 1992. A Global Malaria Strategy was agreed upon and endemic countries committed themselves to strengthening already existing malaria control

efforts and initiating others in order to reduce the disease burden at every level. The strategy aimed to curb socio-economic loss due to malaria by preventing mortality and reducing morbidity and by progressively improving and strengthening the local and national capabilities for the control of malaria at all levels.

The two main objectives set were as follows:

1. appropriate malaria control programmes had to be implemented by 90% of the countries affected by the year 1997
2. malaria morbidity was to be reduced by at least 20% compared to 1995 in at least 75% of the affected countries, by the year 2000 (WHO, 1993).

Unfortunately, the strategy has not been successful for many of the countries involved. Most countries lacked adequate financial resources and appropriate technical capabilities necessary for the successful implementation of malaria control programmes (WHO, 1993).

In 1998, the Roll Back Malaria (RBM) partnership was initiated to provide a coordinated global approach to fighting malaria. RBM is a partnership between WHO, UNDP, UNICEF and the World Bank, whose aim is to mobilize support for local and national malaria control initiatives worldwide. It seeks to work with governments, NGOs, and private sector companies to reduce the human and socio-economic costs of malaria. RBM is promoting strategies that are evidence-based, outcome focused and cost-effective (WHO, 1998). These include four main strategies as follows:

1. Prompt access to treatment

2. Insecticide-treated mosquito nets
3. Prevention and control of malaria in pregnant women
4. Malaria epidemic and emergency response

The partnership set the following goals: to halve the burden of malaria worldwide by the year 2010 and halve that again by 2015 using control tools which already exist and need wider dissemination, or which can rapidly be developed (WHO, 1998). Consequently, African governments, including Kenya, held a summit in Abuja-Nigeria in 2000 and adopted the Abuja Declaration, including the target to protect at least 60% of children less than five years of age with the most suitable combination of personal and/or community protective measures such as ITNs by 2010 (WHO/CDS/RBM, 2002).

Current Vector control strategies

In 2004 WHO launched the Global Strategic Framework for Integrated Vector Management (IVM). It provides a basis for strengthening vector control in coordination with national health systems. IVM advocates an evidence-based approach to the utilisation of national resources and encourages community engagement to ensure sustainability. It provides for integration with other disease control measures and the systematic application of a range of interventions for vector control (WHO, 2004a).

Use of ITNs

Most malaria-endemic countries in Africa have focussed their attention on scaling up the use of ITNs as the most reliable malaria prevention strategy

in children < 5 years of age. By the early 1990s, it had been shown that ITNs were safe to use and effective in reducing malaria transmission (Lines et al., 1987, Curtis et al., 1992, Lines, 1996). In the Gambia, an experimental study combining the use of chemoprophylaxis and ITNs reported a pronounced reduction in mortality in children less than five years of age. The study found that malaria-specific mortality was reduced by 70% and all-cause mortality was reduced by 63% (Alonso et al., 1991a, Alonso et al., 1991b). The fact that the overall mortality of a community could be markedly reduced by the use of ITNs was confirmed by several large-scale randomised controlled trials, which had child mortality as a primary endpoint (D'Alessandro et al., 1995, Binka et al., 1996, Nevill et al., 1996, Habluetzel et al., 1997, Phillips-Howard et al., 2003a). A Cochrane review concluded that the overall mortality in African children would be reduced by 17% as a result of ITN use (Lengeler, 2004). Such a reduction translates into 6 lives saved in a year for every 1000 children aged between 1 and 59 months. Furthermore, the mortality study in western Kenya (Phillips-Howard et al., 2003b), which was then an area of intense perennial transmission, demonstrated a 90% reduction in malaria transmission and the EIR was reduced from 60-300 to below 10 (Gimnig et al., 2003). In this same study, ITNs were also found to have a positive impact on birth weight and on the growth of infants (ter Kuile et al., 2003a, ter Kuile et al., 2003b). A recent systematic review of the impact of ITNs in pregnancy involving five randomized controlled trials in sub-Saharan Africa found that using ITNs in the first few pregnancies reduced the occurrence of low birth weight by 23% compared to non-use of nets (Gamble et al., 2007).

ITNs generally need to be treated with insecticide approximately once a year, in order to maintain their effectiveness (Lines, 1996, Maxwell et al., 2003). In a field situation, many difficulties are encountered in trying to maintain high re-treatment levels. Effectiveness projects in Africa have indicated an average re-treatment rate below 10%. The recent introduction of Long Lasting Treated Nets (LLTNs) has been a breakthrough in solving this problem. LLTNs can resist several washes and remain efficacious for their useful lifespan. Some brands of LLTNs recognized by the World Health Organization Pesticide Evaluation Scheme (WHOPES) include the Olyset Net (Sumitomo Chemical Co., Osaka, Japan), Perma-Net (Vestergaard Frandsen A/S, Kolding, Denmark) and Interceptor (BASF). The Permanet and Interceptor nets are made from polyester cloth and the nets are expected to last for 3-5 years. The Olyset net is made from polyethylene fibres and lasts >5 years (The Global Fund, 2007).

Increased national and international efforts have now boosted the deployment of ITNs. Most of the African countries, including Kenya, have waived taxes and tariffs on nets, netting materials and insecticides. Since 2002, several countries have scaled up free of charge or subsidized provision of ITNs for children under 5 years of age and pregnant women (UNICEF, 2007). A new approach to increase net coverage has involved nationwide campaigns to boost measles vaccination and provision of vitamin A, coupled with the distribution of free LLTNs (Grabowsky et al., 2005, Grabowsky, 2008). As a result, there has been a substantial increase

in net coverage in the countries involved, according to household surveys that measured either ITN usage by children < 5 years of age or household ownership (WHO/GMP, 2007).

Use of IRS

IRS has been found to be highly effective to achieving a temporary, rapid reduction in malaria transmission. The main purpose of indoor residual spraying is to reduce transmission by reducing the survival of malaria vectors entering houses or sleeping units (Global Malaria Programme World Health Organisation, 2006). The information available suggests that its impact in areas of intense malaria transmission in reducing infant and child mortality is similar to that reported with ITNs (Curtis and Mnzava, 2000).

Despite its initial widespread use and contribution to the success of malaria eradication and control efforts, the use of IRS declined in most malaria endemic countries in the last decades, particularly in Africa. This was in part due to lack of government commitment and financing to sustain the logistically challenging efforts over the long term, but also due to concerns about insecticide resistance and community acceptance. One of the other reasons was the general disapproval of dichlorodiphenyltrichloroethane (DDT), the most widely used insecticide, due to fears of its harmful effects on the environment and on human health. In the past, DDT was widely used in agriculture and domestic hygiene, leading to massive release of the compound into the environment (Global Malaria Programme World Health

Organisation, 2006). Some authors now have a renewed opinion that these fears are unjustified when DDT is used appropriately for IRS (Global Malaria Programme World Health Organisation, 2006, 2006, Mandavilli, 2006, Rehwagen, 2006, Schapira, 2006, Guimaraes et al., 2007, Sadasivaiah et al., 2007, Curtis and Lines, 2000, Curtis, 2002). Whereas, others argue that DDT may do more harm than good in the long run and that it is not the only answer to malaria control (Berenbaum, 2005). In 2004, the Stockholm Convention on Persistent Organic Pollutants became operational in order to enforce strict control measures to reduce environmental damage from organic pollutants; however it stated that the use of DDT was still required in some countries for disease vector control (UNEP, 2001).

In the last five years IRS has received renewed attention and WHO now recommends that effective implementation of IRS with DDT, or one of the 11 other recommended insecticides, should be a central part of national malaria control strategies where this intervention is appropriate. IRS is recommended only when the following conditions are met: a high percentage of the structures in an operational area have adequate sprayable surfaces, and can be expected to be well sprayed; the majority of the vector population is endophilic (rests indoors); and the vector is susceptible to the insecticide in use (Global Malaria Programme World Health Organisation, 2006). About half of African countries have included IRS as part of their malaria control strategies (WHO and UNICEF, 2005),

and several more have now included IRS as part of the President's Malaria Initiative (PMI) funded malaria control initiatives.

The lack of progress in the development of new insecticide compounds suitable for public health use coupled with increasing vector resistance has resulted in a dwindling availability of alternative low-risk and cost-effective insecticides, which may threaten the sustainability of IRS. The recognition that there is an urgent need to develop new and cheap alternative insecticide for public health use (WHO and UNICEF, 2005) has led to recent initiatives like the Gates funded Innovative Vector Control Consortium led by LSTM. In addition systematic monitoring for insecticide resistance is needed, requiring new levels of funding to set up or enhance existing insecticide resistance surveillance systems and new levels of international collaboration (Kelly-Hope et al., 2008).

Drug based control

Treatment of malarial infections

The other cornerstone of malaria control programs has been case management of clinical or microscopy-confirmed malaria. The rapid spread of resistant strains of the malaria parasite to chloroquine in the 1980s in Africa resulted in a clear rise in recrudescence of infection and persistence of anaemia (Bloland et al., 1993, Ekvall et al., 1998). This link between resistance and chloroquine treatment failure is likely to have contributed to the increase in malaria-specific mortality that was observed in endemic countries in the 1990s (Trape et al., 1998, Snow et al., 2001).

The arrival of highly-effective artemisinin-based drug combinations, although costly, brought desperately needed alternatives for case-management. WHO now strongly recommends that endemic countries change their policies to adopt artemisinin-based combination therapy as first line treatment for uncomplicated malaria (World Health Organisation, 2006). The high cure rate achieved with these combinations (White, 1994, White, 2008c, Adjuik et al., 2004) and the prospect of sustained efficacy is likely to markedly reduce the malaria burden. This has been observed in Thailand (Carrara et al., 2006) and in South Africa (Barnes and White, 2005). In the latter, the introduction of ACTs was also associated with other control measures such as the use of bed-nets and indoor residual spraying (Tren, 1999).

Most malaria-endemic countries have now switched their policies to use artemisinin-based combination therapy as first line treatment (World Health Organisation, 2006). In 1999, the WHO set itself the goal of halving the rate of malaria mortality worldwide by 2010. Improvement of accessibility and affordability of effective chemotherapy in general and artemisinin-based combinations in particular is more crucial than ever for reducing the malaria burden in endemic countries.

Mass drug administration to prevent malaria

Administration of anti-malarial drugs to an entire population has been used as a malaria-control strategy for decades (von Seidlein et al., 2003). Drugs

were given to all individuals, whether infected or not, at specific points in time, either directly as a full therapeutic course of treatment or indirectly through the fortification of salt, with the main aim of minimizing the reservoir of infection (von Seidlein and Greenwood, 2003). In highly or moderately endemic countries where most infections are asymptomatic and go untreated, it seems unlikely that an impact on transmission could be achieved using only mass drug administration (MDA). In a recent comprehensive review, von Seidlein and Greenwood report that the first attempts of malaria control through MDA date back to the early 1930s in rubber plantations in Liberia, West Africa (von Seidlein and Greenwood, 2003). In the 1950s, MDA was adopted by WHO as a control tool, until the 1970s when it was finally dropped due to its failure to interrupt transmission of malaria and to the role it may have played in the spread of chloroquine resistance (WHO, 1993). Later in 1999 in the Gambia, a cluster randomized controlled trial attempted to reduce transmission of malaria at the start of the transmission season through one single administration of artemisinin plus sulphadoxine-pyrimethamine (von Seidlein et al., 2000). Residents living in 33 of 42 villages in the catchment area received a single dose of sulphadoxine-pyrimethamine combined with artesunate, whereas residents of 9 control villages received placebo. For the first two months following the MDA, the mean malaria incidence rate in treated villages was significantly lower than in the control villages. However, in subsequent months, the incidence was slightly higher in the MDA villages (rebound effect), and no overall cumulative benefit of MDA was detected over the course of the malaria transmission season.

In summary, most MDA, which have been undertaken as part of an attempt to interrupt transmission, have failed. However, despite a failure to achieve this objective, many MDA projects led to a marked reduction in parasite prevalence and probably had a marked transient effect on malaria-related morbidity and mortality, although this was rarely measured. Currently the use of MDA is mostly restricted to special situations such as epidemics as was the case in Burundi in 1999 (Etchegorry et al., 2001, Evans, 2001).

Anti-malarial chemoprophylaxis

There is clear evidence that chemo-prophylactic use of anti-malarial drugs can substantially prevent the consequences of malaria in at-risk groups in pregnant women and children under five years of age (Geerligs et al., 2003, Meremikwu et al., 2008, Garner and Gulmezoglu, 2006). Chemoprophylaxis can be defined as the administration of anti-malarial drugs to targeted groups of people, at sub-therapeutic dosages, so as to obtain sustained protective blood levels over the period at risk. This implies that the drugs are used before infection occurs or before it becomes patent, with the aim of preventing either the occurrence of the infection or any of its symptoms. Some drugs act on the early stages of the parasite, while it is still confined to the liver, and destroy these stages before merozoites are liberated into the blood stream and infect red blood cells. In such cases, Bruce-Chwatt defines the relevant drug as a true prophylactic (Bruce-Chwatt, 1980). When the drug is unable to achieve this effect and yet, if given for a prolonged period (exceeding the normal duration of the incubation period), it is able to keep the number of malaria parasites in the blood at such low

levels that they will not cause any clinical symptoms, then it acts, as a suppressive (or clinical) drug (Bruce-Chwatt, 1980). In practice, this means that when the drug administration is discontinued, any parasites remaining in the blood start multiplying again and this may lead to a renewed attack of the disease. The rapid excretion of most drugs that have been used for chemoprophylaxis means that frequent administrations are needed (e.g. on a daily, weekly or fortnightly basis). For this reason, anti-malarial drugs used for chemoprophylaxis should have a long half-life so that the dosing interval can be extended. Until recently, the drugs available for chemoprophylaxis were limited to chloroquine, proguanil, pyrimethamine + dapson, mefloquine, atovaquone-proguanil and doxycycline. The latter three are now the most commonly used options for travellers in the prevention of falciparum malaria.

Chemoprophylaxis in children

Several studies have investigated the impact of chemoprophylaxis on the health of young children living in malaria-endemic areas. The first data were reported in 1956 from the Gambia (McGregor et al., 1956). In that study, chloroquine was given to children under three years of age. The strategy significantly improved malaria morbidity. Other studies came to the same conclusions; chemoprophylaxis reduced the incidence of clinical episodes of malaria, and increased haemoglobin concentration whilst improving nutritional indices (Bradley-Moore et al., 1985a, Bradley-Moore et al., 1985b, Bradley-Moore et al., 1985c).

Chemoprophylaxis also substantially reduced mortality. In a study of Gambian children aged between three months and five years conducted in 1988, Maloprim (pyrimethamine + dapsone) given every 2 weeks throughout the transmission season resulted in a marked reduction in the incidence of overall deaths, deaths attributed to malaria and in the incidence of clinical episodes detected through active surveillance (Greenwood et al., 1988). In that study, the protective effect of chemoprophylaxis was sustained over a period of five years until the study was stopped, when it was considered to be unethical to continue (Menon et al., 1990). The impact of chemoprophylaxis was reviewed in detail recently, the results suggested fewer episodes of clinical malaria, and a reduction in severe anaemia and hospital admissions (Meremikwu et al., 2008).

Chemoprophylaxis in pregnant women

In areas with stable malaria transmission, immunity to malaria develops after exposure to the parasite for a number of years and complications in the adult population are rare. During pregnancy however, women become more susceptible to malaria, and may present with different clinical features of malaria infection during pregnancy, depending on the degree of immunity that they may have acquired by the time they became pregnant. In areas of high transmission, malaria infection in pregnant women tends to be asymptomatic and associated with maternal anaemia and low birth weight (Desai et al., 2007).

The use of anti-malarial drugs for chemoprophylaxis to prevent *P. falciparum* infection in pregnant women was first reported from Nigeria in 1964 using pyrimethamine (Morley et al., 1964). Though this was initially highly effective, high levels of parasite resistance finally rendered this approach ineffective. Weekly chloroquine prophylaxis was proposed as an alternative, but with increasing levels of resistance and poor adherence, this has been found to be inadequate in the majority of the countries where it has been tried (Mola and Wanganapi, 1987). Proguanil was found to be safe in pregnancy but needed to be given daily, and needed to be preceded by effective parasite clearance (Mutabingwa et al., 1993). Fortnightly Malarone has been shown to be effective in increasing birth-weight and reducing anaemia in primigravidae in the Gambia (Greenwood et al., 1989). Weekly and fortnightly chemoprophylaxis during pregnancy with efficacious anti-malarial drugs was shown to reduce maternal anaemia and the proportions of low birth weight babies within controlled trials (Garner and Gulmezoglu, 2006). In the Gambia, reduction of low birth-weight by chemoprophylaxis led to an estimated reduction in the neonatal death rate by 42% and infant mortality by 18% among primigravidae, and by 6% and 4% respectively among children of multigravidae (Greenwood et al., 1992). The most recent Cochrane meta-analysis also suggest that successful prevention of malaria during pregnancy results in significant reduction in peri-natal deaths by 27% (which includes pregnancy loss from 28 weeks gestation onwards and neonatal death within the first 7 days) (Garner and Gulmezoglu, 2006).

Limitations of chemoprophylaxis

Sustaining a high compliance with chemoprophylaxis in either children or pregnant women has proved difficult to achieve within national control programmes. Furthermore, concerns about the possible impact of long-term chemoprophylaxis on the development of natural immunity to malaria have been one of the main reasons for reluctance to pursue this strategy. It would not be sensible to protect a child from malaria for a period of time if the risk of dying from the disease is increased to the same degree after the drug administration is stopped. It has been shown by several authors that children who received repeated drug administration for a long term had lower titres of anti-malarial anti-bodies compared to children who did not (Bradley-Moore et al., 1985a). Menendez and others during a study conducted in 1995 in Ifakara, in South-eastern Tanzania showed that chemoprophylaxis during the first year of life was effective in prevention of malaria but impaired the development of natural immunity as there was a rebound in the incidence of clinical malaria and anaemia in the second year of life (Menendez et al., 1997, Aponte et al., 2007). Other authors suggested that the impairment of the natural immunity is strongly dependent on the duration of the prevention. According to Otoo and others, chemoprophylaxis can act to reduce but not prevent exposure to the parasite, and this can overcome some suppressive effects of malaria on cell-mediated immunity, and thus induce a better development of cellular immune response to malaria antigens (Riley et al., 1988, Otoo et al., 1989).

In the late 1990s WHO dropped their recommendation for implementation of chemoprophylaxis on a large scale due to its potential for a rebound effect; logistical challenges to delivery, relatively high cost of implementation; low compliance with long-term regimens and the potential impact on the spread of drug resistance.

IPT in pregnancy (IPTp)

History

In 1994 in Malawi, it was shown that sulphadoxine-pyrimethamine given only twice during pregnancy (one dose in the second trimester and one dose in the third trimester) was more effective at reducing placental parasitaemia than weekly chloroquine (Schultz et al., 1994). A 72% reduction in placental malaria (from 32% to 9%) in primigravidae and secundigravidae was observed. Subsequent studies in Kenyan primigravidae living in Kilifi district showed a 39% (95% CI 22-52%) protective efficacy of intermittent preventive treatment with sulphadoxine-pyrimethamine in preventing severe anaemia (Shulman et al., 1999). Parise and others came to the same conclusions as they found intermittent sulphadoxine-pyrimethamine treatment in the second and third trimester to be a highly efficacious way to prevent placental malaria infection in Kenyan primigravidae (Parise et al., 1998). On the basis of these results, the WHO recommended that all pregnant women resident in areas of moderate to high malaria transmission should be given intermittent preventive treatment with sulphadoxine-pyrimethamine throughout the second and third trimesters of pregnancy (WHO, 2004b, WHO, 2005). This recommendation

has been adopted by most of the malaria-endemic countries in Africa and replaced weekly chloroquine chemoprophylaxis which had been used until then as the drug based strategy for prevention of malaria during pregnancy (WHO, 2007).

Concept

Intermittent preventive treatment during pregnancy consists of administration of treatment doses of an efficacious antimalarial drug given at predefined intervals at least 1 month apart, regardless of the presence of malaria parasitaemia at the time of treatment. Intermittent preventive treatment during pregnancy provides intermittent clearance or suppression of existing asymptomatic infections from the placenta (treatment effect) and when drugs with a long elimination half-life like sulphadoxine-pyrimethamine are used they may prevent new infections from occurring for several weeks due to the slow elimination of suppressive drug levels in the body (prophylactic effect). Another possibility is that sulphadoxine-pyrimethamine may not fully prevent the establishment of new blood-stage infections post-treatment but is able to suppress parasite multiplication to low-density infections that may induce persistent immunity (ter Kuile et al., 2007, Greenwood, 2007). Intermittent preventive treatment during pregnancy is delivered at the time of routine ante-natal visits and currently sulphadoxine-pyrimethamine is the only anti-malarial recommended for use. The World Health Organization recommends that at least 2 curative doses of sulphadoxine-pyrimethamine be given during the second and third trimesters of pregnancy in areas of stable *P. falciparum* malaria transmission (WHO, 2004b).

Ter Kuile and colleagues recently conducted a systematic review of currently available data to determine the effect of increasing resistance to sulphadoxine-pyrimethamine on the efficacy of intermittent preventive treatment during pregnancy in Africa. The pooled studies showed that in areas in which 1 of 4 treatments with sulphadoxine-pyrimethamine fail in children by day 14, the 2-dose IPT regimen with sulphadoxine-pyrimethamine continues to provide substantial benefit to Human Immunodeficiency Virus (HIV)-negative semi-immune pregnant women. They also showed that more frequent dosing is required in HIV-positive women not using Cotrimoxazole prophylaxis for opportunistic infections. (ter Kuile et al., 2007). The studies which were reviewed in the above mentioned article had been used by WHO's Regional African Office to issue a statement on the continued use of sulphadoxine-pyrimethamine for intermittent preventive treatment during pregnancy in Africa (WHO, 2005). However, high priority must be given to determining safe and affordable alternatives due to the emerging spread of high-grade resistance to sulphadoxine-pyrimethamine. A series of multicentre trials are planned in that regard (Menendez et al., 2007a) but it will take several years before the results of these trials will become available.

IPT in Children (IPTc)

The concept of intermittent preventive treatment in children or IPTc (also labelled seasonal sIPTc when provided in the malaria transmission seasons only) has been proposed as an alternative mechanism for malaria

prevention in areas with highly seasonal transmission (Greenwood, 2006).

One published trial of intermittent preventive treatment in children has been published to date. The study was based in Senegal and used a single dose of sulphadoxine-pyrimethamine plus a single dose of artesunate given at monthly intervals for three months during the malaria transmission season.

The intervention resulted in an 86% protective efficacy against clinical malaria in children 2 to 59 months of age (Cisse et al., 2006). A subsequent study in the same region compared 4 drug combinations; one dose of sulphadoxine-pyrimethamine (SP) plus one dose of artesunate (AS) (SP+1AS), one dose of SP plus 3 daily doses of AS (SP+3AS), one dose of SP plus three daily doses of amodiaquine (AQ) (SP+3AQ) or 3 daily doses of AQ and AS (3AQ+3AS) (Sokhna et al., 2008). Participants were treated once a month for 3 months during the peak malaria season. The study found that all 4 regimens reduced the incidence of malaria but SP+3AS was the most efficacious, and was recommended in order to minimize the spread of drug resistance allowing for AS to reserved for the treatment of acute malaria cases (Sokhna et al., 2008). In neighbouring Mali, another IPTc study with single dose of SP found 43% reduction in the annual incidence rate of clinical malaria (Dicko et al., 2008). The potential benefits of IPTc are substantial, particularly in areas with seasonal transmission where malaria affects children up to five years of age. More research is needed to determine if this is a practical approach to malaria control, particularly to address the feasibility of scaling up an intervention that does not build on any existing healthcare platform could prove challenging, and secondly, to address whether the administration of multiple closely spaced

doses of antimalarial drugs covering a short transmission season impede the development of natural immunity to *p. falciparum* (Greenwood, 2006, Grobusch et al., 2007a).

IPT in infants (IPTi)

The concept and history of IPTi

Concept

In 2001, the IPT approach was adapted to the prevention of malaria in infants (IPTi) by Schellenberg and colleagues in the first IPTi trial in Tanzania (Schellenberg et al., 2001). IPTi was designed in an effort to harness the benefits of chemoprophylaxis while minimizing the problems. By linking the delivery of the intervention to the already well established routine vaccination visits, the logistic and delivery considerations were considerably eased. It was also anticipated that, because fewer doses are given than would normally be used in chemoprophylaxis, the concerns about cost, drug resistance and immunological effects would be reduced.

In the first randomized, double-blind, placebo-controlled trial in Ifakara in Tanzania, a single dose of sulphadoxine-pyrimethamine (SP) was administered on three occasions during the first year of life at 2, 3 and 9 months of age, at the routine vaccination visits in the Expanded Programme of Immunization (EPI). IPT was given regardless of whether or not the study subject had malaria symptoms or parasitaemia (Schellenberg et al., 2001).

The study found the intervention to be highly effective. The rate of clinical malaria (events per person-year at risk) was 0.15 in the intervention arm versus 0.36 in the placebo arm, giving a protective efficacy of 59% (95% CI 41-72%). A 50% reduction of severe anaemia in the intervention arm was also observed at the end of the study. With the limitation of a small sample size, the trial did not show any adverse reactions to sulphadoxine-pyrimethamine and indeed, an extended follow-up of the trial participants until age 2 years showed a sustained reduction in the risk of clinical malaria extending well beyond the duration of the pharmacological effects of the drugs (protective effect 36%, 95% CI 11-53%), (Schellenberg et al., 2005). Thus, study investigators were able to demonstrate a clinically and statistically significant decrease in malaria-related morbidity by linking IPTi delivery to existing public health interventions that serve as a routine contact point for health-workers and children world-wide.

In another study conducted also in Tanzania, Massaga and colleagues studied two hundred and ninety-one infants aged 12-16 weeks who attended Maternal and Child health clinics in a district where malaria is perennial (Massaga et al., 2003). For a period of six months, these infants were given a treatment course of amodiaquine or placebo every 60 days. The authors showed that the protective efficacy of intermittent treatment with amodiaquine in preventing malaria fevers was 64.7% (95% CI 42.4-77.2%; $p < 0.001$).

The encouraging results of the first trial of intermittent preventive treatment led some healthcare workers to consider implementation on a wide scale (Schellenberg et al., 2006). Others suggested that it was important to balance the urgency of implementing a new, efficacious intervention on a public health scale against the need to acquire convincing evidence on safety and efficacy, and it was agreed that further evaluation of IPTi was necessary.

The IPTi Consortium

The evidence available by 2002 was reviewed by a group of research scientists and representatives from WHO and UNICEF. This group agreed that information was required in three key areas before intermittent preventive treatment could be recommended as a national malaria control strategy.

1. Firstly, better knowledge of its efficacy in reducing malaria morbidity in different epidemiological settings.
2. Secondly, a clear demonstration that it had no adverse impact on serological responses to EPI vaccines.
3. Thirdly, that all safety data available on intermittent preventive treatment with sulphadoxine-pyrimethamine be consolidated and evaluated (Egan et al., 2005).

The IPTi Consortium was established in 2003 with support from the Bill and Melinda Gates Foundation to further the development and evaluation of IPTi. The Consortium comprises 14 institutions working as seven research

collaborations (Table 1: Institutions currently participating in the IPTi Consortium) across Africa and Papua-New Guinea, and includes WHO and UNICEF.

Table 1: Institutions currently participating in the IPTi Consortium

1. Albert Schweitzer Hospital, Lambarene, Gabon
2. Centers for Disease Control and Prevention, Atlanta, USA
3. Hospital Clinic, University of Barcelona, Barcelona, Spain
4. Ifakara Health Research and Development Centre, Ifakara, Tanzania
5. Kenya Medical Research Institute, Kisumu, Kenya
6. Kilimanjaro Christian Medical Centre, Moshi, Tanzania
7. London School of Hygiene and Tropical Medicine, London, UK
8. Manhica Health Research Centre, Manhica, Mozambique
9. National Institute for Medical Research, Amani, Tanzania
10. Swiss Tropical Institute, Basel, Switzerland
11. Universite Cheikh Anta Diop de Dakar, Dakar, Senegal
12. University of Copenhagen, Copenhagen, Denmark
13. University of Tübingen, Tübingen, Germany
14. United Nations Children's Fund (UNICEF)
15. World Health Organization (WHO)
16. Papua New Guinea Institute of Medical Research

(Note: Trials are carried out in collaboration with local malaria control programmes and ministries of health.)

Research Agenda IPTi Consortium

The IPTi Consortium aims to generate the scientific evidence required to support a policy recommendation on the intermittent preventive treatment of infants in a timely manner. Studies undertaken by the Consortium were planned to answer the above mentioned key questions and designed to run almost parallel to each other in order to facilitate rapid consolidation of the required information.

Studies with SP

The complexities of malaria epidemiology required an evaluation of treatment efficacy in settings with different transmission intensities. Sites were identified in West Africa (Gabon and Senegal), East Africa (Kenya and Tanzania), Southern Africa (Mozambique) and Papua New Guinea. The Consortium is also conducting a large-scale operational research project in southern Tanzania and, in conjunction with UNICEF, is carrying out limited implementation of IPTi in six other countries.

Alternative antimalarials

In addition, a set of Consortium studies were designed to identify the optimal characteristics of drugs and drug combinations suitable for use in IPTi, including the comparison of long-acting (e.g. mefloquine, sulphadoxine-pyrimethamine) and short-acting (e.g. chlorproguanil-dapsone) anti-malarial drugs, with and without the antimalarial artesunate.

Other studies

The effect of IPTi on immunological responses to *P. falciparum* infection, the development of anti-malarial drug resistance, acceptability, cost and cost-effectiveness were also addressed as part of the various studies.

Working groups were set up to coordinate the different aspects being studied by the Consortium. All the studies were subject to clinical monitoring to ensure the quality and integrity of the data they generate.

Summary results from recent IPTi studies with SP

To date, a set of five IPTi trials have been completed that explored the safety and efficacy of using SP for IPTi in addition to the original trial by Schellenberg and colleagues (Schellenberg et al., 2001, Macete et al., 2006, Chandramohan et al., 2005, Kobbe et al., 2007, Mockenhaupt et al., 2007, Grobusch et al., 2007b). The studies were conducted across a range of different malaria-transmission settings in Mozambique, Ghana (3x) and Gabon.

Results from all studies are now available (Table 2, Page 37). The study by Macete et al. in Manhica in Mozambique used a 3, 4, and 9 month treatment schedule and reported a reduction in clinical malaria of 22% but no significant effect on anaemia (Hb <8g/dL). However, there were significant reductions in all- cause hospital admissions (19%) and anaemia hospital admissions after dose 1 and 2 (Macete et al., 2006). In Navrongo in Ghana, Chandramohan et al., administered 4 courses of IPTi at months

3, 4, 9, and 12 and found a protective efficacy against all episodes of malaria of 25% up to 15 months of age, and a reduction in anaemia hospital admissions by 35%. The authors did not find an effect on the prevalence of anaemia (Hb <8g/dL) during the intervention period, however, and reported an increase in cases of high parasite density malaria (≥ 5000 par/ μ L) in the treatment group (-20%) during the period from 16 to 24 months of age (Chandramohan et al., 2005). Two other studies by Kobbe et al. in Kumasi in Ghana and by Mockenhaupt et al. in Tamale, also in Ghana, used a 3, 9, and 15 month schedule and reported a 20% (Kobbe et al., 2007) and 23% (Mockenhaupt et al., 2007) protective efficacy against clinical malaria respectively. The study in Kumasi did not see an effect on the prevalence of anaemia during the intervention period but reported an increase in anaemia in the treatment group after the last dose of study drug. The study in Tamale reported a 24% reduction in the prevalence of anaemia during the intervention period but also saw an increase in anaemia and high parasite density malaria in the treatment group after the last dose of study drug. A study in Lambarene in Gabon obtained a statistically non-significant effect against malaria and a 25% reduction in the prevalence of anaemia during the intervention period (Grobusch et al., 2007b).

With respect to adverse event monitoring, the trial in Kumasi, Ghana, reported two cases of severe skin reactions in the treatment group (both Stevens Johnson Syndrome (SJS)), and one moderate skin reaction in the placebo group, whereas Tamale reported one case of a moderate skin reaction in the treatment group. All the study subjects involved fully

recovered. There were no reports of any other drug related adverse events or any adverse impact on serological responses to EPI vaccines.

Table 2: Description of completed IPTi studies by the IPTi with SP

Study parameter	Schellenberg et al.	Chandramohan et al.	Macete et al.	Kobbe et al.	Grobusch et al.	Mockenhaupt et al.
Trial, country	Ifakara, Tanzania	Navrongo, Ghana	Manhica, Mozambique	Kumasi, Ghana	Lambarene, Gabon	Tamale, Ghana
Recruitment year(s)	1999–2000	2000–2002	2002–2004	2003–2005	2004–2005	2003
EIR/year	29	418	38	400	50	NA
Transmission	Perennial	Highly seasonal	Perennial with seasonal peaks	Perennial	Perennial with seasonal peaks	Perennial with seasonal peaks
Incidence rate per year of clin. malaria* in PL	0.43	1.0	0.55	1.29	0.22	0.88
In-vivo SP Rx-failure by day 14	31 (1999–2000)	22 (2004)	21 (2001)	NA	21 (2004)	14 (2002)
Use of bed nets, % PL/SP ITN (non-ITN)	67/68	17/19	0/0 (14/15)	20/20 estimate (39/38)	5/5 (80/80)	<1%
Iron supplementation	Yes	Yes	None	None	None	None
Ages at IPT dosing, months	2, 3, 9	3, 4, 9, 12	3, 4, 9	3, 9, 15	3, 9, 15	3, 9, 15
Method and duration of follow up	PCD to 24 months of age (CSS at 12 and 18 months of age)	PCD to 24 months of age (CSS at 2, 9, 12 and 18 months of age)	PCD to 24 months of age (CSS at 12 and 24 months of age)	ACD monthly to 21 months of age and PCD	ACD monthly to 30 months of age and PCD	ACD every 3 months to 24 months of age and PCD
enrolled children, placebo/Rx-group	351/350=701	1242/1243=2485	755/748=1503	535/535=1070	595/594=1189	600/600=1200
PE, % (95% CI)	By 12 months	By 15 months	By 12 months	By 18 months	By 18 months	By 18 months
Clin. malaria (all episodes)	62.3 (44.2, 74.6)	24.8 (14.3, 34.0)	22.6 (1.6, 39.2)	20.3 (10.6, 28.9)	17.0 (-24.0, 44.0)	22.5 (11.8, 31.9)
Clin. malaria (high density)	67.8 (48.8, 79.8)	23.6 (11.1, 34.3)	26.4 (5.1, 42.9)	18.5 (5.0, 30.2)		17.7 (2.0, 30.9)
All-cause hospitalisations	30.0 (8.1, 46.6)	12.7 (-4.8, 27.3)	19.0 (4.0, 31.0)	8.7 (-23.4, 32.4)		31.3 (13.1, 49.9)
All-cause severe anaemia	50.3 (7.6, 73.2)	35.5 (11.2, 53.1)	12.7 (-17.3, 35.1)	NA	22.0 (-1.0, 40.0)	23.6 (4.1, 39.1)
Rebound effect	None: sustained effect (10 to 24 months)	Yes: more high-density parasitaemia in 16 to 24 month old children	None: (10 to 24 months)	None: (16 to 24 months)	None:	Yes: more severe malaria (13 to 24 months)

IPTi, intermittent preventive treatment delivered to infants; ACD, active case detection; PCD, passive case detection; EIR, entomological inoculation rate; CSS, cross-sectional surveys; PL, Placebo: clinical malaria*, all episodes; Rx, Treatment; NA, Not applicable; high density (≥ 5000 par/ μ L).

Meta-analysis

The IPTi Consortium has conducted a pooled safety and efficacy analyses of all six trials of IPTi with sulphadoxine-pyrimethamine conducted to date at 12 months of age (Breckenridge et al. and Aponte et al., in preparation).

Efficacy

The pooled analyses have shown a 30% protective efficacy against malaria, a 23% protective efficacy against all-cause hospital admissions, a 38% protective efficacy against malaria-related hospital admissions, and a 15% protective efficacy against anaemia (Hb <8g/dL), all in the first year of life (Grobusch et al., 2007a). The trials were not powered to measure the effect of IPTi on mortality but it was noted that the total number of deaths in the treatment groups and the placebo groups was similar (Breckenridge et al. in preparation). One death in the six trials was considered possibly attributable to sulphadoxine-pyrimethamine (Kobbe et al., 2007). Overall, there was a 19% significant reduction in the risk of serious adverse events (SAE) (which, by definition, included any hospital admissions and deaths) among the treatment groups compared to the placebo groups across all the trials. Only the skin reactions earlier mentioned above were noted.

Safety

WHO convened a committee to investigate possible interactions between IPTi and the serological response to EPI vaccines, which found no difference in the geometric mean titre between the treatment and placebo groups for measles, diphtheria, pertussis, tetanus, polio, hepatitis B and yellow fever. It concluded that IPTi with sulphadoxine-pyrimethamine

administered at the time of routine vaccination does not have an adverse impact on the serological responses to EPI vaccines when co-administered with them (Grobusch et al., 2007a).

The Kumasi, Tamale and Navrongo trials that reported some rebound in the second year of life did not represent an overall consistent pattern of rebound. Navrongo reported some rebound in high density clinical malaria, Kumasi recorded rebound in the number of anaemia episodes (Hb <8g/dL), and Tamale observed rebound in severe malaria and severe anaemia (Hb <5g/dL) (Kobbe et al., 2007, Chandramohan et al., 2005, Mockenhaupt et al., 2007). Furthermore, in the pooled meta-analyses, there was no significant rebound in episodes of clinical malaria, anaemia, or all-cause hospital admissions or with parasites in the five month period after the IPTi schedule was completed.

Conclusions IPTi studies with SP

Thus, the interim results of these analyses suggest that IPTi with sulphadoxine-pyrimethamine offers a modest level of protection against malaria morbidity in the first year of life, and in contrast to earlier chemoprophylaxis trials, is not associated with a rebound effect based on the currently available evidence. Thus, it appears to offer protection against malaria and anaemia while not interfering with the acquisition of natural immunity to *P. falciparum* (Grobusch et al., 2007a). The Consortium already provided a considerable dossier of scientific evidence to a specially

convened WHO study group as part of a platform for IPTi-related policy discussions. These findings are currently under consideration by WHO.

Remaining questions

Effect on development of immunity against malaria

Clearly another important question with regard to the mode of action is whether and how protection in the first year of life may affect the development of malarial immunity. It is not clear why the first trial showed a much higher protection in the first year of life (almost twice as much) than the subsequent trials and observed persistence of protection in the second year of life, whereas the subsequent trials did not (Gosling et al., 2008).

The six studies differed in transmission intensity; transmission seasonality; timing of dosing of the study drug; timing of the assessment of main end points; parasite resistance to the study drug; other illnesses or nutrient deficiencies affecting anaemia; coverage with other malaria prevention and treatment interventions, such as iron supplementation and the use of insecticide-treated bed nets; and other features not measured or reported (Ter Kuile and Steketee, 2006). Of note is that the initial study in Tanzania had the highest ITN coverage of all trials and had the highest level of sulphadoxine-pyrimethamine resistance. It has been hypothesized that that this initial study was conducted during a one-off situation with a unique combination of favourable factors like transmission intensity, ITN use, and moderate parasite resistance to the drug. Moderate resistance may have resulted in persistence of low grade parasitaemia that escaped drug action. This combined with reduced levels of transmission and thus potentially

overwhelming re-infections may provide a vaccine type of effect that translated into long-lasting protective immunity that may not be readily reproducible in other situations (ter Kuile et al., 2007, Greenwood, 2007, Grobusch et al., 2007a). It may also be that the results were at the higher end of the normal variation of protective efficacy, with subsequent trials showing regression toward the mean. Similar observations were seen with the large-scale ITN trials that were conducted in the 1990s. An alternative explanation for the difference in observed effects of IPTi between sites and the extended period of protection into the second year of life observed in the Ifakara study may be a decrease in malaria transmission during the study period, as recently suggested by Gosling et al (Gosling et al., 2008). It is hoped that the ongoing pooled analysis of the extended follow-up of the studies may help to shed some light on the complex interplay between the various potential determinants of protective efficacy such as transmission intensity and use of ITNs.

Drug resistance

Two concerns have been raised regarding IPTi and drug resistance. Firstly, how the implementation of IPTi with sulphadoxine-pyrimethamine will affect parasite resistance to the drug. There is no doubt that widespread use of sulphadoxine-pyrimethamine for treatment led to selection of resistant parasites. Mutations found in the DHFR and DHPS genes involved in the parasite folate pathway are associated with parasite resistance to sulphadoxine-pyrimethamine (Roper et al., 2003). These mutations have been associated with reduced efficacy of sulphadoxine-pyrimethamine for

treatment of uncomplicated malaria in children <5 years of age (Omar et al., 2001, Kublin et al., 2002). This has been well documented in in-vivo studies right across the African continent (Schellenberg et al., 2002, Mockenhaupt et al., 2005, Abacassamo et al., 2004, Allouche et al., 2004, Oduro et al., 2005). The IPTi Consortium is currently investigating the relationship between widespread use of sulphadoxine-pyrimethamine for IPTi and molecular markers of drug resistance in a large-scale study in Tanzania involving 12,000 infants.

Secondly, how does the in-vivo measure of efficacy of a drug relate to its efficacy in intermittent preventive treatment in infant studies? It appears that sulphadoxine-pyrimethamine continues to be effective in IPTi despite high rates of resistant haplotypes and its reduced efficacy when used for treatment of symptomatic malaria. It seems that at the current levels of sulphadoxine-pyrimethamine resistance, there is no clear correlation between the protective efficacy of sulphadoxine-pyrimethamine used as intermittent preventive treatment and treatment efficacy. It has thus been hypothesized that the mechanism of action in sulphadoxine-pyrimethamine may be different in the context of prevention as opposed to treatment (Grobusch et al., 2007a). Although this is likely to be true, the studies to date in both infants and pregnant women have all been conducted at times of low to moderate resistance to sulphadoxine-pyrimethamine as measured from the treatment responses in concurrent treatment trials in children with acute falciparum malaria. It is unlikely that sulphadoxine-pyrimethamine will have much effect on clearing existing infections or preventing new

infections once high grade resistance is well established (e.g. wide spread presence of the 164L mutation) (ter Kuile et al., 2007, White, 2005).

Alternative drugs for IPTi: Target Product Profile (TPP)

Thus, there are justified concerns about the longevity for sulphadoxine-pyrimethamine as the drug of choice for IPT in pregnancy or infants because of the increasing levels of antifolate resistance. Studies of alternative drugs are urgently required. One of the first steps in this process is the development of a target product profile (TPP) to determine the optimal and desirable characteristics of a drug regimen suitable for use in intermittent preventive treatment. Judging from the available literature and ongoing debate on IPTi, it would seem that a suitable drug would, as a pragmatic choice, have a dosing regimen ≤ 3 days (ideally a single dose), and would have to be efficacious, safe and well tolerated, whereas the optimal drug would have a single dose regimen, be very efficacious, very safe and extremely well tolerated.

Mode of action involved in IPTi

One of the other key questions in defining the target product profile is the mode of action of IPTi. For example, understanding how intermittent preventive treatment with sulphadoxine-pyrimethamine achieves its protective effect may help to address whether long or short acting drugs are required for IPT (Greenwood, 2007).

Sulphadoxine-pyrimethamine prevents the establishment of new blood-stage infections by producing inhibitory blood concentrations for approximately 4 to 8 weeks after administration of each curative dose depending of the level of resistance of the parasites (White, 2005, Watkins et al., 2005, Watkins and Mosobo, 1993). Evidence from the recent pooled analyses of the IPTi consortium by month of follow-up suggests that the effect of intermittent preventive treatment could be largely related to intermittent chemoprophylaxis (the prophylactic effect) rather than clearance of parasitaemia only. A more detailed analysis of the study in Navrongo also suggests that this prophylactic effect does not last for longer than the pharmacological effect of sulphadoxine-pyrimethamine (Cairns et al., 2008). If the above is true then a long-acting alternative drug would be more suitable and efficacious for use in intermittent preventive treatment than a short-acting drug. It would be possible to demonstrate this concept in a study that would compare the efficacy of drug regimens with markedly different half-lives.

Studies comparing short versus long-acting drugs

The IPTi Consortium has been investigating the safety and efficacy of alternative drugs and drug combinations to sulphadoxine-pyrimethamine for use in IPTi through other trials designed to explore those issues. Two of those trials, Kisumu in Kenya (described in this thesis) and Kilimanjaro in Tanzania, were designed to compare short-acting versus long-acting drugs when used for IPTi. In 2003, when these studies were being designed the following drugs were available and considered as suitable candidates:

sulphadoxine-pyrimethamine plus artesunate, mefloquine, amodiaquine plus artesunate, and chlorproguanil-dapsone. The Kisumu trial chose to assess the following drugs: sulphadoxine-pyrimethamine plus artesunate, amodiaquine plus artesunate, and chlorproguanil-dapsone. The Kilimanjaro trial chose to assess the antimalarials sulphadoxine-pyrimethamine, mefloquine, and chlorproguanil-dapsone.

Whereas, a short-acting drug is rapidly eliminated from the body and therewith only able to provide a treatment effect (clearance of existing infections), a long-acting drug is one that is slowly eliminated from the body so that it has a suppressive effect on malaria re-infection for a period of time after treatment. The duration of that period (post-treatment prophylaxis) is determined by the dose, pharmacokinetic properties of the drug, and the level of parasite resistance to the drug (White, 2008a). For the short-acting drug, chlorproguanil-dapsone (CD) was selected based on demonstrated efficacy in Kenya (Watkins et al., 1988, Winstanley et al., 1997) and northern Tanzania (Mutabingwa et al., 2005). CD has a terminal elimination half-life ($t_{1/2}$) of between 6 to 19 hours (Hietala et al., 2007). The two long-acting antimalarials given in combination with short-acting artesunate were AQ and SP. Amodiaquine had been shown to be efficacious for IPTi in neighbouring Tanzania (Massaga et al., 2003), and for treatment in western Kenya (Vreugdenhil et al., 2004). The desethyl metabolite of AQ, which accounts for nearly all antimalarial activity, has a $t_{1/2}$ of between 3 to 12 days (Barnes et al., 2006). Sulphadoxine has a $t_{1/2}$ of 7 days, whereas pyrimethamine has a $t_{1/2}$ of 3 days (Adjuik et al., 2002). Artesunate (AS) was added to both SP and AQ because of uncertainties of

how rising *P. falciparum* resistance to SP and AQ alone might compromise efficacy if the primary action of IPTi was due to parasite clearance.

Available data suggest that AQ plus AS is more efficacious than AQ alone in the treatment of uncomplicated malaria in symptomatic African children (Gupta et al., 2002, Doherty et al., 1999). Similarly, SP plus AS is more efficacious than SP alone (Obonyo et al., 2003, von Seidlein et al., 2000, Targett et al., 2001, Beutler et al., 1989). Artesunate is very short-acting and has a $t_{1/2}$ of approximately 1 hour (White, 2005), and was not added to CD because of the very high treatment success rate observed with CD in Kenya and northern Tanzania, and because at the time there were no published studies on the safety or efficacy of a CD plus AS combination.

Chapter 3: Country and site of study

Introduction to the study country

Geography

Kenya is located in East Africa (Figure 1, Page 50) and lies between latitudes 4.21 0 N and 4.28 0 S and between longitudes 34 0 E and 42 0 E. It is bisected into almost half horizontally by the Equator and vertically by the 38 0 E meridian lines. The total land area is 592,909 square km which includes 11,230 km² of inland water which is mainly comprised of Lake Turkana and Kenya's section of Lake Victoria (Snow, 1999).

Demography

The current population is estimated to be to 38 million in 2008 (CIA, 2008). The population distribution varies from 230 persons per square kilometre in agricultural high potential areas to 3 persons per square kilometre in arid areas. The population is relatively youthful with 41% of the population being under the age of 15 years on the basis of the 2004 population census. The number of persons aged over 65 years represented about 4% of the population in 2004 (compared to 18% < 15 years and 15.7% over 65 years in the United Kingdom in the same year (US Census Bureau International Data Base (IDB), 2008)).

Climate

Kenya's climate varies from a tropical climate on the coast characterized by hot and humid conditions to a temperate climate inland and to a dry climate in the north. Over 70% of the country is arid and semi arid receiving little annual precipitation while rainfall is greatest in the highlands. Most parts of the country experience a bimodal pattern of rainfall, with the long rains coming in March- May and the start of the short rains occurring through October to December. Altitude is a major factor in variations in temperature between the different regions of the country. Average temperature ranges in the coastal town of Mombasa (altitude 17 metres) from 22°C to 30°C, in the capital city Nairobi (altitude 1680 metres) from 11°C to 28°C, and in Kisumu (altitude 1070 metres) on the shores of Lake Victoria from 17°C to 35°C.

The epidemiology of malaria in Kenya

Malaria is a major public health problem in Kenya. The malaria burden and transmission patterns vary across the country from highly endemic to epidemic-prone. Overall, the diversity of the Kenyan climate lends itself to a wide variation in malaria risk and subsequent disease epidemiology. There are four principal groupings that can be used: endemic, highland (epidemic prone), arid (epidemic prone), and low risk districts (Snow et al., 1998). Modelling suggests that malaria accounts for approximately 30% of all outpatient attendance and 19% of all admissions to health facilities. It is reported to be one of the leading causes of death of children under age 5, responsible for an estimated 13.6% of deaths (Snow et al., 1998). Each

year, an estimated 26,000 children (that is 72 per day) die from the direct consequences of malaria infection. An estimated 170 million working days are lost to the disease each year (Snow et al., 1998).

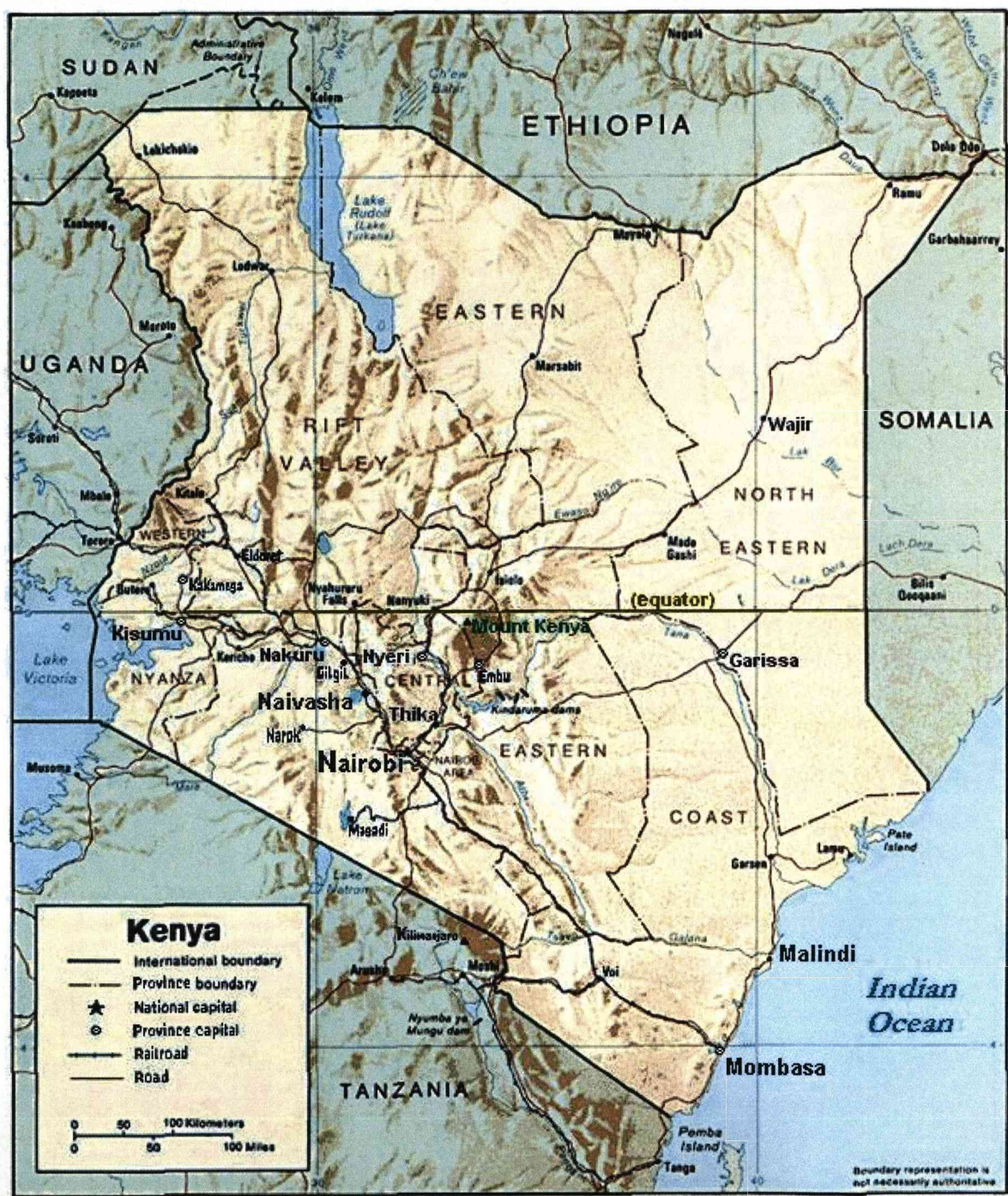
Malaria control in Kenya

The Division of Malaria control was established in the year 2000 as the operational arm of the National Malaria Control Programme at the national level. The objective of the Division at its inception in 2000 was to reduce the level of malaria infection and consequent death toll in Kenya by 30% by the year 2006 and to sustain that improved level of control to 2010.

To achieve this, four main strategic approaches have been used i.e.

1. Clinical management.
 - Providing effective and prompt treatment
 - Management of malaria and anaemia in pregnancy
2. Vector control using ITNs and other methods
3. Epidemic preparedness and response (including indoor residual house-spraying (IRS))
4. Supporting structure
 1. Information, Education and communication (IEC)
 2. Monitoring, evaluation and research.

Figure 1: Map of Kenya



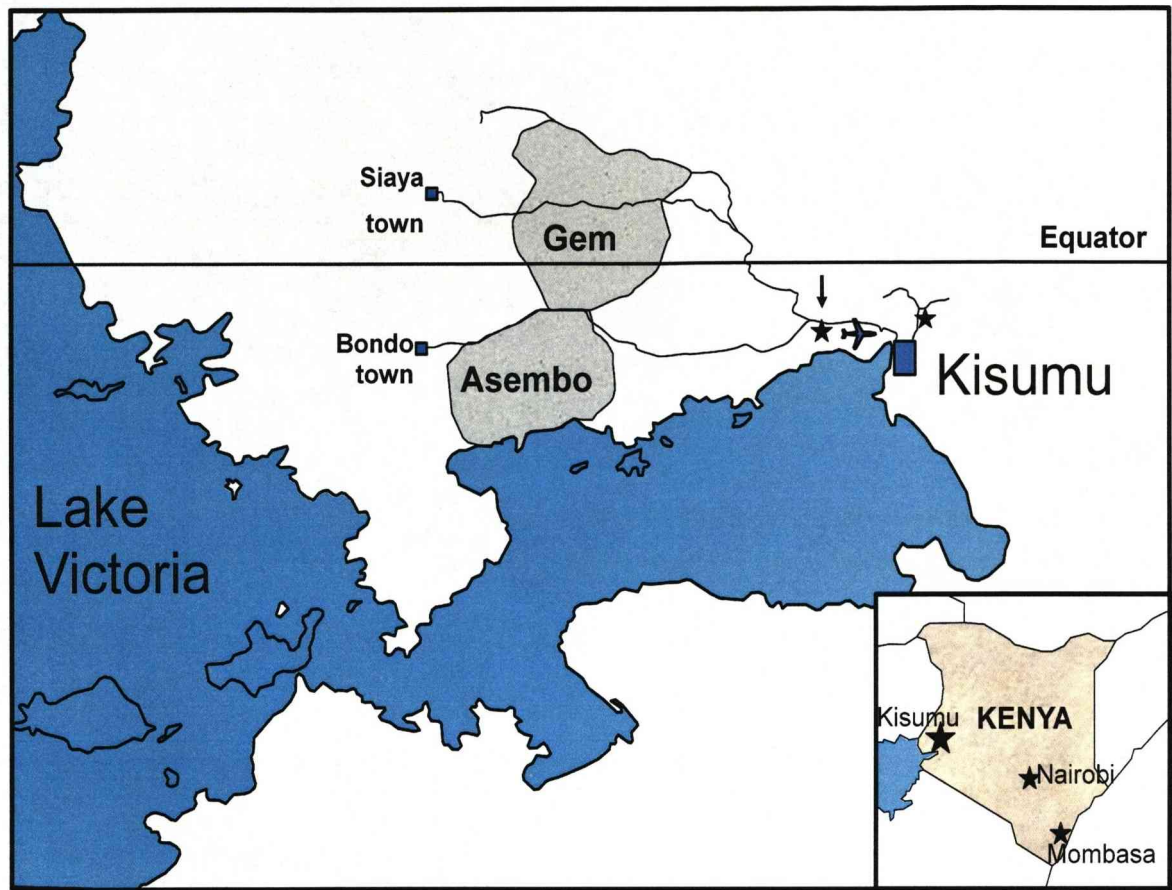
Introduction to the study area

Location

The study took place in Asembo (Rarieda Division, Bondo District, Nyanza Province), western Kenya (Figure 2); the total population is approximately

55,000 persons living in 76 villages in an area covering 178 square kilometres (Phillips-Howard et al., 2003a, Adazu et al., 2005).

Figure 2: Location of Asembo in Western Kenya



Social structure and economy

The population is culturally homogeneous (more than 95% are of the Luo ethnic group and this proportion recently increased further due to the migration of internally displaced persons after the recent tribal clashes following the disputed general elections in December 2007) and they live in dispersed settlements. Most of the houses (Figure 3 and Figure 4) are built of mud, cement, or brick with roofs of iron sheets or thatch. Agricultural fields tend to lie adjacent to the compounds. The mainstay of the local economy is subsistence farming, occasionally boosted with meagre incomes from trading in the local food and livestock markets. Rainfall is

Chapter 3: Country and site of study

seasonal with the heaviest (long) rains usually occurring from March through May and short rains falling between October and December. Local crops include maize, sorghum, cassava, and millet. Because employment opportunities are limited, many young adults temporarily migrate to the urban areas to seek employment.

Figure 3: Mud and cement houses with iron sheet roofing



Figure 4: Mud-house with thatched roofing



Health care infrastructure

The area is served by 2 district hospitals (Bondo and Kisumu) between 10 and 60 km from the study area, and 1 small mission hospital (without surgical facilities) located in the centre of the study area (Lwak). There are 6 “health care units” located in Asembo. These units are comprised of government, community, and private facilities and are normally staffed by an enrolled community health nurse. Only one of the health care units (a government Health Centre) is staffed by a Clinical Officer and a registered nurse, and has diagnostic facilities for malaria.

Epidemiology of malaria in the study area

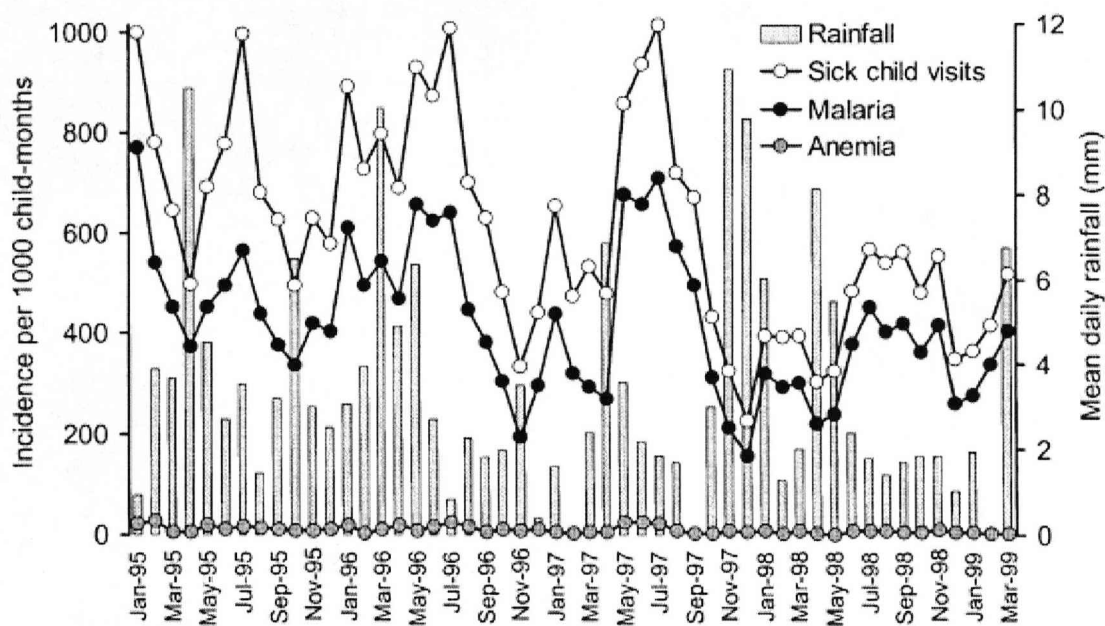
This lowland area around Lake Victoria experienced intense perennial malaria transmission (Beier et al., 1990). Although transmission occurs

throughout the year there is clear seasonal variation with two seasonal peaks reflecting the normal bimodal rainfall pattern. The heaviest rains fall from March through May (long rains) with a smaller peak (short rains) in November and December (Figure 5) (Phillips-Howard et al., 2003a). Most transmission is due to *Anopheles gambiae* and *An. funestus*, with the proportion of infections attributed to each species varying both spatially and temporally. The small remaining balance of transmission is due to *An. arabiensis*.

Over the past 15 years, this area has been the site for a variety of malaria related research projects conducted by the KEMRI/CDC research unit in Kisumu, and the epidemiology of malaria has changed considerably. Transmission rates were reduced by 90% during an ITN efficacy trial (ITN population coverage > 70%) conducted from 1996 to 2002 (Gimnig et al., 2003, Phillips-Howard et al., 2003b). The continued provision of free ITNs to the entire population has helped to maintain the low entomological inoculation rate (EIR), currently estimated at 7.2 infective bites per person per year (down from 60-300) (Lindblade et al., 2004, Adazu et al., 2005). Despite the reduced transmission level, cross-sectional surveys conducted in 1999, 2000 and 2001 (during the long rainy season when malaria transmission peaks) reported the prevalence of parasitaemia and moderately severe anaemia (Hb<7g/dL) among children < 5 years of age as 36% and 10% respectively (ter Kuile et al., 2003b, Lindblade et al., 2004). The infant mortality rate changed from 176.1/1,000 live births in 1992, to 110/1,000 live births in 2004, and 72/1,000 in 2007 (Adazu, 2007,

McElroy et al., 2001). Based on verbal autopsy data approximately 30% of infant deaths are attributed to malaria (Adazu et al., 2005).

Figure 5: Trends in rainfall, sick child visits, and diagnoses of malaria and anaemia at seven peripheral health facilities, before and during the insecticide-treated bed net intervention in 1996 to 1999.



From (Phillips-Howard et al., 2003a).

Antimalarial treatment policy and drug resistance

SP became the first-line antimalarial drug for the treatment of uncomplicated malaria in Kenya in 1998. Data from 1999-2000 demonstrated that the adequate clinical and parasitological response (ACPR) by day 28 for SP was 54% among children aged <5 years in neighbouring Bondo, western Kenya (Obonyo et al., 2003). In 2000, the treatment response to amodiaquine monotherapy in symptomatic children <5 years was reported as 89% in Bungoma, western Kenya (Vreugdenhil et

al., 2004). A more recent study in 2007, in Bondo, western Kenya reported similar high (90%) ACPR for amodiaquine-artesunate (Thwing, 2007). The available data on chlorproguanil-dapsone sensitivity show 98% ACPR in coastal Kenya in 1997, but no data were available from western Kenya by the start of the study (Amukoye et al., 1997). However, chlorproguanil-dapsone was not readily available locally and its relatively limited use probably resulted in low drug pressure. In 2005, during the course of this trial, the Kenyan Ministry of Health (MOH) adopted artemether-lumefantrine (AL) as the first line treatment for uncomplicated malaria (Kenya, 2006), though implementation began in late 2006.

Vaccine coverage

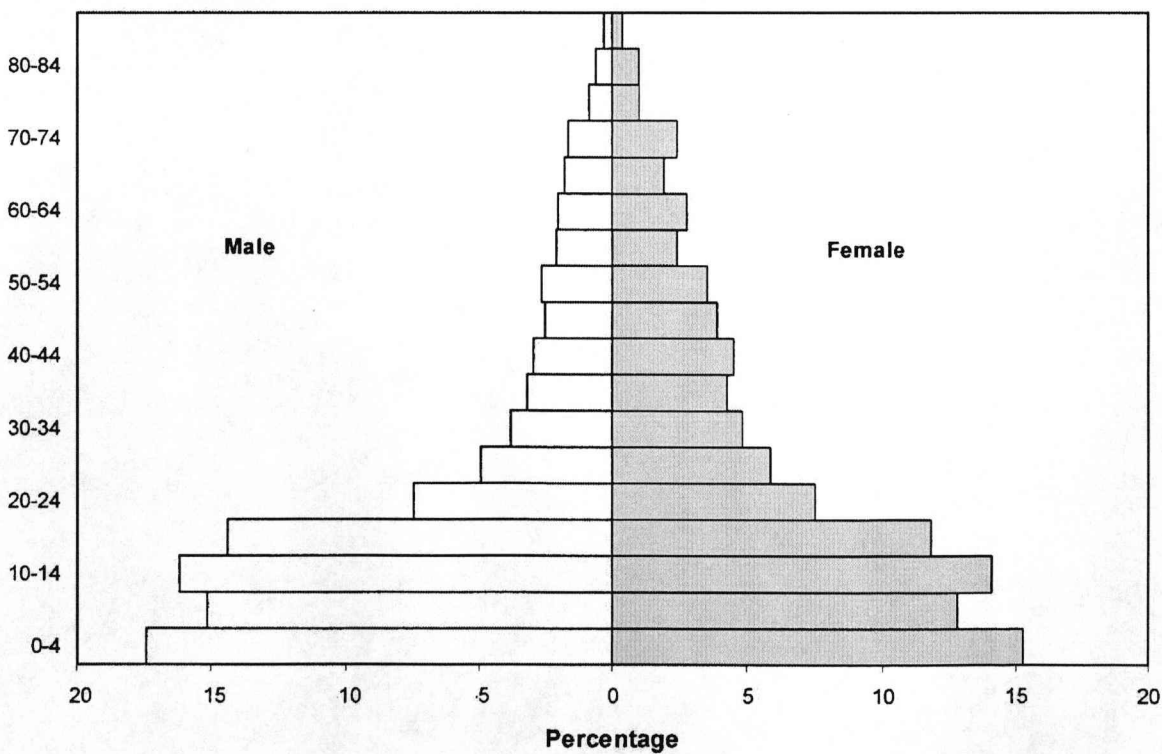
EPI coverage in the study area is relatively poor: 55% of children receive all three doses of the pentavalent (diphtheria-tetanus toxoid-pertussis-hepatitis B- *Haemophilus Influenza* type b) vaccine and oral polio vaccine (OPV), 48% receive the measles vaccine and only 38% receive all the essential vaccines in the programme, as compared to the national statistics for Kenya which estimate that 73% of children receive the measles vaccine and 57% receive all the essential vaccines (Bureau of Statistics Kenya et al., 2004). The cold-chain required for the successful implementation of the EPI programme is not operational in some healthcare centres in rural western Kenya due to logistical problems forcing those centres to offer vaccination only on a couple of appointed days of the week, further exacerbating an already difficult situation with access to essential services. The ineffective utilisation of such a well established programme is a missed

opportunity to improve primary healthcare and deliver potentially life-saving interventions like IPTi which easily fit into the EPI schedule.

Health and demographic surveillance system (HDSS) in study area

The Health and Demographic Surveillance System (HDSS) provides a platform that facilitates research activities, and allows scientists to measure the burden of infectious diseases and evaluate public health interventions. All the households in the study area are visited every four months and data on the population (Figure 6) educational attainment, socioeconomic status, paediatric outpatient visits, causes of death in children, and malaria transmission are collected (Adazu et al., 2005).

Figure 6: Distribution of population by age (years) and sex in 2002



Research facilities

The Research Station is located at the Centre for Global Health Research of the Kenya Medical Research Institute (CGHR / KEMRI) in Kisumu (Figure 7) (Kenya Medical Research Institute, 2008), Kenya and was established in 1979 by the Division of Parasitic Diseases (DPD), CDC from the US working in collaboration with KEMRI. Over the past 29 years, CDC's investment in the Research Station (Figure 8) has resulted in a well-trained group of staff members of Kenyan scientists, clinicians, laboratory technicians, and field workers. In the past, most of the activities were focused on malaria research. Although malaria research remains a priority at the station, activities have expanded rapidly over the last few years and currently include malaria prevention activities, as well as HIV research, TB Prevention, and HIV prevention and care program activities and are supported by the Global AIDS Program, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the President's Malaria Initiative (PMI). Another focal area is the International Emerging Infectious Diseases Program.

Laboratory and Communications Capabilities

The KEMRI/CDC Research Station has well-developed malaria and HIV laboratories that perform a range of standard diagnostic procedures (serology, haematology, microscopy).

The malaria laboratory (Figure 9) has the capability to perform sophisticated research assays such as polymerase chain reaction (PCR), gene sequencing and microsatellite work, lymphocyte sub typing, and

Chapter 3: Country and site of study

cytokine measurement and is actively engaged in research on parasite diversity and the immunology of malaria in children under five years and pregnant women.

The HIV laboratory (Figure 10) conducts a range of HIV diagnostic tests, including rapid tests, enzyme-linked immunosorbent assay (ELISA), Western blot, BED HIV incidence testing, viral load and infant DNA PCR, CD4 immunology; a variety of chemistry and haematology assays; and diagnostic tests for sexually transmitted infections (Chlamydia, gonorrhoea, syphilis, HSV-2, *Trichomonas vaginalis*) and, using both rapid diagnostic tests and ELISA, hepatitis B and C. The HIV research laboratory also has the capacity to perform HIV drug resistance testing and HIV sub typing.

The microbiology laboratory performs primary isolation and identification of enteric organisms (*Vibrio cholerae*, *Shigella*) and respiratory organisms (*Streptococcus pneumoniae*) as well as antimicrobial susceptibility testing for these pathogens. Research on the immunology of schistosomiasis is also conducted.

Figure 7: KEMRI director's office



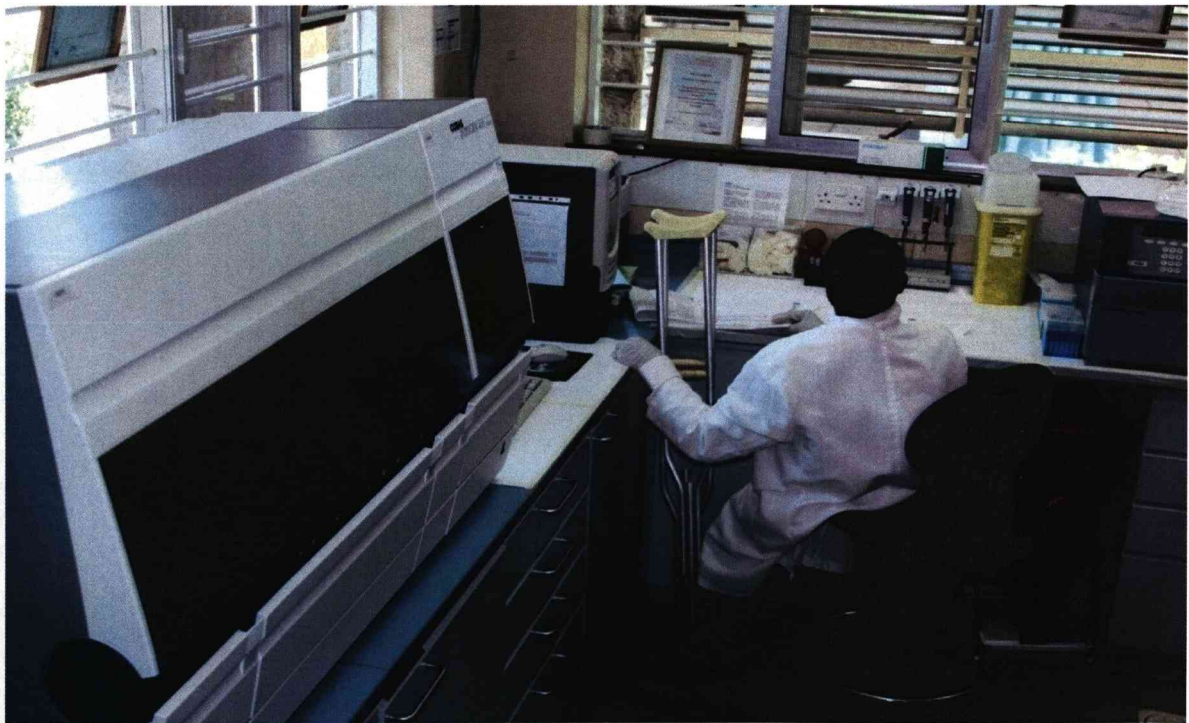
Figure 8: Main administrative office and IT centre



Figure 9: Malaria Laboratory work-space



Figure 10: HIV Laboratory work-space



Chapter 4: Materials and methods

Overview study design

We conducted a randomized double-blind, placebo-controlled efficacy trial (RCT) among children under longitudinal observation to estimate the efficacy and safety of IPTi with short and long-acting antimalarial drugs administered at the time of routine EPI vaccinations (at 10, 14 weeks and 9 months), in order to understand the mechanism of action of IPTi (treatment vs. prophylactic effect). Children were recruited during the first EPI visit at 6 weeks of age and were followed prospectively with collection of epidemiologic, clinical, and laboratory data. Routine EPI visits in Kenya occur at 6, 10, and 14 weeks, and again at 9 months of age. IPTi was provided under supervision at 10 and 14 weeks and again at 9 months with one of 3 drug regimens or a placebo. From ages 2.5-6.5 months, supplementation with ferrous sulphate was given as part of the intervention package.

The 4 arms of the study were as follows:

- I Intermittent sulphadoxine-pyrimethamine+ three doses of artesunate treatment with daily iron supplementation;
- II Intermittent chlorproguanil-dapsone treatment with daily iron supplementation;
- III Intermittent amodiaquine+ three doses of artesunate treatment with daily iron supplementation;
- IV Intermittent placebo treatment with daily iron supplementation.

Morbidity surveillance was achieved through scheduled visits to the clinics and passive case detection, and anaemia and parasitaemia cross-sectional surveys at 12, 18, and 24 months of age. Figure 11 depicts the individual trial time-line.

Objectives

Primary objective:

To compare the efficacy of IPTi with one of 3 antimalarial regimens (sulphadoxine-pyrimethamine+ three doses of artesunate [SP-AS3], or amodiaquine+ three doses of artesunate [AQ-AS3], or chlorproguanil-dapsone [CD3]) given at routine immunization visits with that of placebo with respect to the prevention of clinical malaria in the first year of life.

Secondary objectives:

- 1) Compare the efficacy of IPTi with one of 3 antimalarial regimens (SP-AS3, AQ-AS3 or CD) given at routine immunization visits with placebo with respect to the prevention of moderate and severe anaemia in the first year of life.
- 2) Assess the impact of IPTi with the aforementioned regimens on serologic responses to vaccines (Polio, Diphtheria, Tetanus, Pertussis, Hepatitis-B, Haemophilias-Influenza type-B, and Measles).

Pre-trial activities

Several meetings were held with local administration personnel, opinion leaders and village elders at “Barazas” (official Chief’s meeting at the sub-location level). Meetings were also arranged with parents (mostly women were present) in villages within a 3.5 kilometre radius of each of the four clinics used as study sites. These meetings were designed to “request for permission” to engage the community in research activities, prepare them for mobilisation activities, explain the purpose of the study and answer any questions raised.

In order to achieve a high level of community acceptance for trial activities most of the support staff were hired from within the community after rigorous interviews to select the best candidates were conducted in Asembo. Conducting the trial at four different sites necessitated a larger than anticipated work force (Appendix I) and very intensive training in order to ensure compliance with standard operating procedures (SOPs) at all sites. Study staff was trained on how to follow GCP guidelines and how to fill in scan-ready study forms (Appendix II) among several other study activities. Training remained ongoing throughout the study and GCP refresher courses were given twice every year by the trial monitor. My training as the trial coordinator was even more rigorous, involving GCP requirements, preparation of SOPs, documentation of study activities, adverse event reporting, updating the study regulation files, preparing for monitoring visits among several other responsibilities.

Study population

Infants aged 5 to 16 weeks attending any one of the 4 study clinics (Abidha, Ongielo, Lwak, and Saradidi in Asembo) for immunization at the 6-week visit was offered enrolment in the study if they fulfilled the inclusion and exclusion criteria

Inclusion and exclusion criteria

Inclusion criteria:

1. Age 5 weeks to 16 weeks (this extended period was allowed in consideration of a local cultural custom practiced by a section of the community belonging to the 'Nomiya' religious sect, which involves the detention of newborns indoors for up to 10 weeks).
2. Parent or guardian currently resident in Asembo (or Gem).
3. Parent or guardian has given permission for their child to participate

Exclusion criteria:

1. Known allergy to any of the study drugs
2. Current Cotrimoxazole prophylaxis
3. Concomitant disease requiring hospitalization or transfusion
4. Plans to be away from the study area for more than 6 months during the next year

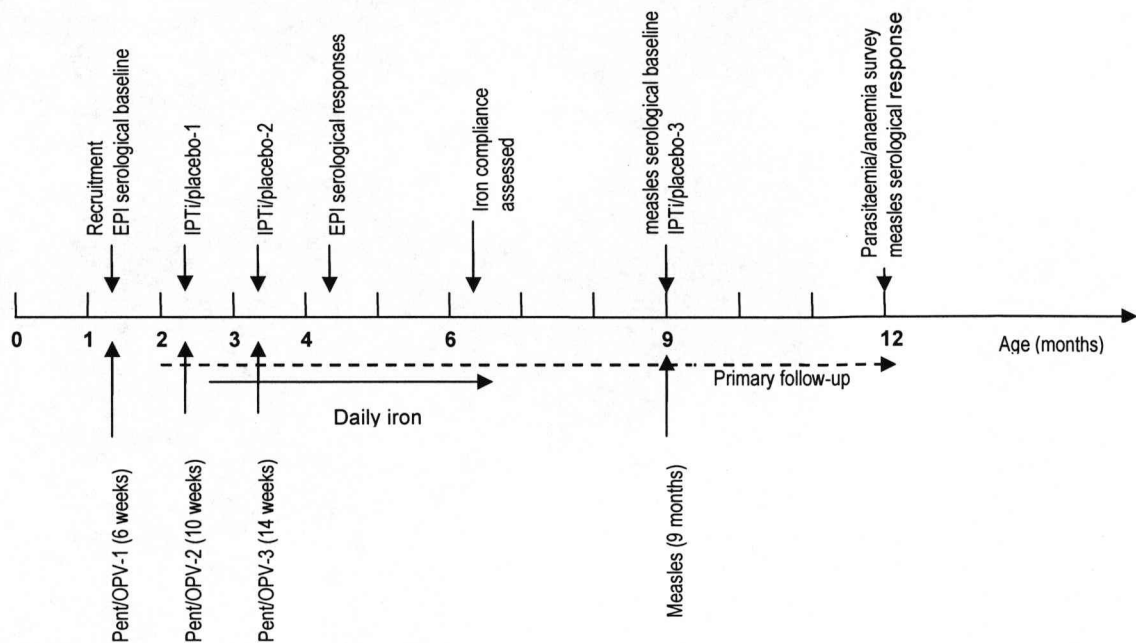
Study Schedule

Table 3: Study Schedule

	6 w	10 w	14 w	18 w	6 m	9 m	12 m	18 m	24 m
Enrolment	X								
Clinic visit	X	X	X	X		X	X	X	X
Sickle Cell screening							X		
Blood draw for G6PD testing		X							
Study drug given		X	X			X			
Malaria Blood film							X	X	X
Haemoglobin							X	X	X
Anthropometric measurements		X					X	X	X
Vaccinations	X	X	X			X			
Blood for serology (antibody testing)	X			X		X	X		
NP swab Hib						X			
Iron Compliance					X				
Filter paper blood spot		X					X		

Note: w, weeks; m, months; NP, nasopharyngeal swab; Hib, *Haemophilus influenzae*

Figure 11: Individual trial time-line for participants of IPTi



Note: Pent=diphtheria-tetanus toxoid-pertussis-hepatitis B-*Haemophilus influenza* type B; OPV=oral polio; EPI=expanded programme of immunization; IPTi=intermittent preventive treatment of infants; Primary follow-up period lasted from approximately 2 months of age up to 12 months of age.

Outcome measures

The primary outcome was time to the first or only episode of clinical malaria in the first year of life. An episode of clinical malaria was defined as an axillary temperature of at least 37.5°C or history of fever in the preceding 48 hours together with asexual *Plasmodium falciparum* parasitaemia of any density.

Secondary outcomes included: in the first year of life.

1. mild anaemia defined as Hb<11g/dL
2. moderate-to-severe anaemia defined as Hb<8g/dL
3. serologic responses to EPI vaccines
4. clinical malaria with >5,000 parasites/ μ L of blood
5. all episodes of clinical malaria
6. all-cause outpatient visits
7. all-cause hospitalisations
8. hospitalisations with malaria illness
9. hospitalisations with moderate-to-severe anaemia.

Sample size and power calculations

This study primarily aimed to determine if routine intermittent treatment with antimalarials resulted in a reduction in childhood clinical malaria. The time to first episode of clinical malaria was used as the primary endpoint and used for sample size calculations.

The sample size required to detect a protective efficacy of 40% with 90% power and a α of 0.017 was 250 per arm. The alpha value of 0.017 instead of 0.05 was used in order to account for multiple comparisons (3 arms each compared to the placebo group, Bonferroni adjustment $0.05/3 \text{ tests}=0.017$). Therefore, the study required a total sample of 1000 infants (250 in each of 4 groups). We expected that 11% of infants would have the outcome measure at baseline and thus would be excluded from the primary analysis (Desai et al., 2003). Including this decrease and adjusting for a 10% loss to

follow up and 13% mortality, the study required 1516 infants (379 in each arm).

Randomisation sequence generation

The randomisation code was prepared before the trial began by a statistician (Dr. John Williamson, CDC, Atlanta) using permuted block randomization with a block size of 8.

Randomisation implementation

Enrolment study forms were pre-printed with the already randomised unique study identification numbers and arranged sequentially. After written informed consent was obtained the registrar assigned the lowest available study identification number to the participant.

Randomisation allocation concealment

Each study drug combination was assigned to a colour and then packed into identical bottles labelled only with the colour, the IPTi course number (1, 2, or 3), the day of treatment (day 1, day 2, or day 3), and whether the drug was drug A or B of the combination. In the case of SP/AS3, the first day had two bottles in the pack containing study drug (one containing SP and one containing AS), and the remaining days had one bottle with placebo (instead of SP) and one bottle with AS. In the case of AQ3/AS3, one bottle on each of the three days contained AQ and the other bottle contained AS. In the case of CD3, one bottle on each of the three days contained study drug, and the other bottle contained placebo. In the case of placebo, all the bottles contained placebo.

All medications were dispensed as crushed tablets, in order to ensure accurate dosing. Mixing with cherry syrup was done at the moment of delivery to ensure drug quality and make the medicines more palatable. Labelling was performed by a scientist (Elizabeth Peterson) who was not involved in analyzing data from this trial. The colour-arm assignment of the study identification numbers remained concealed to everyone (including the technician) until the first intervention visit, after which it remained known to the technician only (Figure 12).

Figure 12: Study drugs were packed into identical bottles with different colour labels



Blinding

Doses of the study drugs were prepared in an isolated and locked pharmacy room. The list of study identification numbers linked to a given colour was kept locked and was accessible solely to the pharmaceutical technician preparing doses. The colour-arm assignment of the study identification numbers remained concealed to everyone except the technician. The technician did not have access to names of participants. The key to the colour-arm assignment was kept by a scientist not associated with the study (Dr. Anja Van't Hoog) and the Data and Safety Monitoring Board (DSMB). The key was obtained for analysis in exchange for the locked dataset and detailed analytical plan after the primary follow-up period (the first 12 months of life).

Study procedures

Recruitment of participants

Infants were offered enrolment in the study when they attended a Mother and Child Health (MCH) clinic at any one of the 3 healthcare units in Abidha, Ongielo and Saradidi or the mission hospital in Lwak aged 5 to 16 weeks and resident in Asembo at that time (Figure 13). Infants with known allergy to any of the study drugs, or HIV infected infants receiving cotrimoxazole prophylaxis for opportunistic infections, or infants suffering concomitant illness requiring hospitalization or transfusion, or planning to be away from the study area for more than 6 months were not enrolled. All enrolled children were provided with an ITN and the parent/guardian was

instructed on effective use and maintenance of the net. Damaged nets were replaced during the course of the study.

Figure 13: Mothers attending an MCH clinic



Consenting procedure

All mother's/guardians of children who were eligible for the study were informed about the reason for the study (Figure 14). Each activity and requirement of the study was explained to them. Informed consent forms which had been translated into the local language (Dholuo), and back-translated to check for accuracy were used. In the case of a literate parent/guardian, the entire informed consent form was read out to the parent and repeated if necessary to their satisfaction. The consenter responded to all questions or requested senior staff (like the Field

Supervisor or PI) for further clarification where necessary. Comprehension was assessed using a standard set of questions, and the parent/guardian was requested to sign the form in duplicate for documentation of willingness to participate. The forms were also signed by a witness and the consented parent/guardian retained one copy, whereas the study retained the other. In case the parent/guardian was illiterate, then a literate witness (not connected with the research study) sat all through the consenting procedure and ensured that the consented understood all that was read to them, then the literate witness signed the forms alongside a thumb-print of the consented parent/guardian attesting to the fact that the permission was accurately read or interpreted, and that participation and thumb-printing were given willingly without coercion. All the parents/guardians who were approached were informed that their children's entry into the study was voluntary and that they were free to withdraw from the study at any time.

Figure 14: Mother undergoing consenting procedure



Follow-up procedures

Photographic identification was used to confirm identities at each visit.

Malaria incidence was estimated through passive surveillance. Infants with any illness were instructed to return to one of the study clinics for care,

which was provided free of charge. A rapid diagnostic test (RDT)

(OptiMal®, DiaMed, Switzerland) for malaria was performed for all infants

with a documented fever ($\geq 37.5^{\circ}\text{C}$ by axillary measurement), history of

recent fever in the previous 48 hours, or evidence of pallor. RDT results

were used solely for clinical management and not for trial outcome

measures. The DiaMed OptiMAL® detects the presence of Plasmodium

lactate dehydrogenase (pLDH), an enzyme produced by all forms of the

parasite. The presence of pLDH is revealed using monoclonal antibodies

directed against isoforms of the enzyme. If the RDT was positive, the infant

was treated with oral quinine (10 mg/kg three times daily for 7-day course) or artemether-lumefantrine (Coartem: 1 tablet twice daily for 3 days) for children ≥ 12 months of age weighing >5 kg. If the sick visit and positive RDT occurred at the 10- or 14-week or 9-month visit when study drug was due, then a paired 7-day treatment (prepared for each arm prior to trial commencement) was given such that the arms containing active study drugs were paired with placebo, whereas the placebo arm was paired with quinine. This arrangement ensured that all participants regardless of study arm received appropriate treatment for clinical malaria. In addition, Hb levels were checked and blood slides prepared. Any other childhood illnesses were treated according to the Integrated Management of Childhood Illnesses and MOH guidelines.

Participants who presented with serious adverse events suspected to be attributable to study drugs were withdrawn from receiving further study drugs but follow-up visits and healthcare continued. Those who migrated outside the study area for more than 3 months were suspended from the study but allowed to re-enter upon returning to the study area, or considered lost to follow-up if they failed to return.

Laboratory procedures

Malaria smears

A thin and a thick smear were made on the same slide. The thin smear was used for species confirmation while the thick smear was used for examination and counting of the parasites. The thick smear has the

advantage of concentrating the parasites by approximately 30 times compared with a thin smear.

Only the thin smear was fixed. The top part of the thin smear was not fixed if it was too close to the thick smear. The thin smear was completely covered in methanol for 2 to 3 seconds by dipping the slide in a coplin-jar filled with methanol. The thin smear was allowed to air dry for 2 minutes.

Staining of the blood smears

The slides were put into staining dishes or jars making sure that they were placed back to back in the staining jar to avoid smear-to-smear contact, which could lead to detachment. Working Giemsa solution was poured over the smears until completely covered. The smears were allowed to stain for the 15 minutes in 10% Giemsa (pH 7.2). Clean water was gently poured into the trough or staining jar to float off the scum on the surface of the stain. Care was taken not to wash off the blood smears. The remaining stain was gently poured off and rinsed again 2 times in clean water. The slides were removed from the staining dish or staining jar using forceps. The slides were placed in a vertical position (standing on end) on a staining rack to drain and dry.

Reading and counting procedure

After the slides were completely dry, they were examined one by one under the microscope. After placing a stained slide on the stage, the 40x objective was used to scan the entire thick smear to get a general idea whether the smear was well prepared, well stained and free of debris and artefacts. A

part of the thick smear that was populated with at least 8 White Blood Cells per High Power Field (WBCs/HPF) was selected, the 40x objective was moved from position and a drop of immersion oil applied. The 100x objective was moved into position and focused clearly. The slide was examined using the 100x objective and moved systematically across the field down 1 field and then backwards. This procedure was repeated until the entire blood smear had been examined. If parasites were found, a tentative species determination was made based on the thick smear, and then the thin smear was further examined to confirm the species. The thin smear is the appropriate sample for species identification. After the species had been identified, the asexual parasites (and gametocytes) were counted against 500 WBC on thick smears. Two tally counters were used (1 for parasites and 1 for WBCs). If only gametocytes were present and no asexual parasites, gametocytes were counted against 500 WBCs. The WHO recommends that at least 100 fields, each containing approximately 10-20 WBCs, be screened before scoring a thick smear negative. Assuming an average WBC count of 8,000 per microlitre of blood, this gave a threshold of sensitivity of 4 parasites per microlitre of blood. After examining the slide, it was gently wiped with a cotton wool ball soaked in Xylene, let to dry and stored in a slide cabinet at room temperature.

Determination of parasitaemia

To quantify malaria parasites against WBCs, we counted the parasites in a thick smear. The number of asexual parasites per litre blood (assuming 8,000 WBCs per litre of blood) was quantified by the mathematical formula:

$$\frac{\text{No of parasites} \times 8000}{\text{No of WBCs}} = \text{Parasites per litre}$$

Quality control for smear reading

All slides were read by two laboratory technicians independently, who were blinded to treatment arms. Slides with discrepant readings or with parasite density estimations that differed by >50% were sent to a senior technician for a third reading, the result of which was considered final. All the laboratory technicians involved passed their training organised by the Kenya Medical Research Institute and Walter Reed Project Centre of Excellence in Microscopy situated in Kisumu. The external quality assurance services for the Parasitology and Microbiology laboratories are contracted to the National Institute for Communicable Diseases in South Africa.

Rapid diagnostic test kit (RDT)

DiaMed OptiMAL-IT is an immuno-chromatographic test, using monoclonal antibodies against the metabolic enzyme pLDH (parasite lactate dehydrogenase) of Plasmodium species. These monoclonal antibodies are classified in two groups:

- one specific for Plasmodium falciparum

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- the other is a pan-specific monoclonal antibody which reacts with all species of Plasmodium which can occur in human beings (*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*).

It is important that you do not leave the material exposed to humidity and high temperature. Use the test, according to instructions, within 15 minutes of opening.

Validation of the test

Results are valid if:

- the control band is clearly visible (dense line)
- the reaction field is cleared of blood

Results are not valid if:

- the dipstick is not sufficiently cleared (reaction field remains red)
- the control band is not present
- the control band is not visible even if one or both of the diagnostic bands are present
- the control band and the band "Pf" are present while the band "P" is absent

If the results are not valid, repeat the test, following the test procedure precisely.

Interpretation of results

Negative results

- no detectable line, other than the control band is visible

Positive results

- If all three bands are visible, positive (for *P. falciparum*).

- If the control band and the “P” band is visible, positive (for *P. vivax*, *P. ovale*, or *P. malariae*)

Hb determination using Hemocue® photometers

Capillary blood was collected in micro-cuvettes and examined in Hemocue® photometers (Angelholm, Sweden) to determine Hb levels. The first step of haemoglobin determination begins with the finger stick, performed strictly according to the relevant SOP. Obtain an adequately filled cuvette following the correct procedures. The filled cuvette must be placed in the photometer within 10 minutes of sampling. Measurements made after 10 minutes may result in erroneous Hb estimation.

Daily Quality Control

1. Every day, the Clinic Coordinator or his/her designee tests the calibration control cuvette specific for the HemoCue photometer before patient testing, and after every 20 tests (if there are that many in one day). Values obtained should not deviate from the assigned value on the control cuvette card more than $\pm 0.3\text{g/dl}$. If the reading for the calibration control cuvette deviates from the stated reading, the Field Supervisor is notified immediately.
2. He/she records the date, Hemocue machine number, control cuvette value, reading, and ID code on the Daily Hemocue QC Log.
3. The photometer is designed to work for a long period without any direct service. No everyday preventative maintenance is needed for the electronic components of the photometer. However, the Clinic Coordinator or his/her designee cleans the cuvette holder daily with

70% alcohol or a mild soap solution. The holder must be completely dry before being replaced in the photometer.

4. He/she also cleans the Calibration Cuvette holder on each day of testing and documents on the Daily Hemocue QC Log.

Monthly Quality Control

1. The Field Supervisor brings back the Hemocue machines to the Laboratory for additional quality control every month.
2. The Lab Assistant tests the HemoCue High, Medium, and Low liquid QC reagents monthly.
3. He/she records the date, Hemocue machine number, High, Medium, and Low readings, and their ID code on the Monthly Hemocue QC Log.

All Hemocues® were verified against a Coulter Counter® (Beckman Coulter, USA) at the monthly check-ups in the Laboratory. The external quality assurance services for the Haematology and Coulter Counter equipment are contracted to the United Kingdom National External Quality Assessment Service.

Blood specimens

Capillary blood was also collected at 12 months of age in tubes containing ethylene diamine tetra acetic acid (EDTA) for sickle cell status determination using a standard Hb electrophoresis technique. G6PD mutations at nucleotides 376 (A - G) and 202 (G - A) were detected by polymerase chain reaction followed by digestion with restriction endonucleases *FokI* and *NlaIII* respectively and phenotypes determined from the results (Beutler et al., 1989). Samples for glucose-6-phosphate

dehydrogenase genotypes (G6PD) were collected at enrolment and analysed after all study subjects had completed the primary follow-up period. Table 4 shows how g6pd genotype results were mapped to phenotypes (Beutler et al., 1989).

Approximately, 500 μ L of whole blood was taken by finger prick sampling at the times indicated in Table 3: Study Schedule, Page 66. The samples were centrifuged, and the resulting sera frozen at minus 80 degrees Centigrade. Serum samples were subsequently transferred to the Health Protection Agency, UK for serological assays. The pre-vaccine samples for PENT/OPV were collected at enrolment and the post-vaccine samples one month after the third course of PENT/OPV vaccination and the second course of study drug. The pre-vaccine samples for measles were collected at 9 months of age immediately before the measles vaccination and the third course of study drug, and the post-vaccine samples at the following visit at 12 months of age.

Table 4: G6PD genotypes mapped to phenotypes

MALES	
Genotype	Phenotype
G6PD B	Normal
G6PD A	Mild deficient
G6PD A-	Hemizygous deficient
FEMALES	
Genotype	Phenotype
G6PD B B	Normal
G6PD B A	Normal
G6PD A A	Mild deficient
G6PD B A-	Heterozygous deficient
G6PD A A-	Heterozygous deficient
G6PD A-A-	Homozygous deficient

Investigational drugs

SP-Artesunate

Sulphadoxine-pyrimethamine has been the combination used for IPTi in all previous studies. Sulphadoxine-pyrimethamine has been extensively used in Africa over many years for both the treatment as well as prevention of malaria, and its safety in all age-groups and in later stages of pregnancy is well established (Peters et al., 2007, ter Kuile et al., 2007, Geerligs et al., 2003). For IPTi, approximately 4000 infants received about 12,000 doses of IPTi-sulphadoxine-pyrimethamine in the six trials completed to date. (Grobusch et al., 2007a) Only one trial noted skin reactions considered due

to IPTi; two in the sulphadoxine-pyrimethamine group (both SJS), and one in the placebo group; all three infants recovered fully (Kobbe et al., 2007).

SP was combined with artesunate as part of a loose combination treatment. The rationale for adding an artemisinin derivative was based on the studies that have shown the combination of SP plus artesunate to be more efficacious than SP alone in the treatment of uncomplicated malaria in symptomatic African children (Doherty et al., 1999, von Seidlein et al., 2000, Targett et al., 2001) including in western Kenya (Obonyo et al., 2003).

Amodiaquine-artesunate

AQ was included as an alternative to SP considering rising resistance to the latter and had been shown to be effective for IPTi in Tanzania (Massaga et al., 2003). Amodiaquine (AQ) is a 4-aminoquinoline, structurally related to chloroquine that has been used widely to treat and prevent malaria. It is more palatable than chloroquine and is easy to administer to children. It was first added to the World Health Organization (WHO) Essential Drugs List in 1977, but removed in 1988 for treatment or prophylaxis, because fatal adverse drug reactions were described in travellers using AQ for prophylaxis (Hatton et al., 1986, Neftel et al., 1986, Olliaro and Mussano, 2003) Nevertheless, in the mid 90s amodiaquine was reintroduced in the WHO Treatment Guidelines after it was shown to have good safety and efficacy (Olliaro et al., 1996). Since then it has been widely used in

chloroquine resistance areas as first line treatment of uncomplicated malaria, particularly in west-Africa.

Artesunate was added to amodiaquine because of uncertainties of how rising resistance could affect efficacy of amodiaquine. Amodiaquine is now increasingly deployed in combination with artesunate, one of the artemisinin derivatives. Amodiaquine plus artesunate is more effective than amodiaquine alone (Adjuik et al., 2002, Gupta et al., 2002) and is now used in many countries in loose combination (similar to that used in this study). Recently a fixed combination of artesunate plus amodiaquine was developed by the Drugs for Neglected Diseases initiative with Sanofi-Aventis as the industrial partner. It has been registered in Morocco (the country where the drug is manufactured). A prequalification dossier of this fixed combination has been submitted to the WHO. It is anticipated that the new co-formulation will increase the effectiveness of the combination by improving drug compliance (Sirima and Gansane, 2007). The WHO no longer recommends the use of amodiaquine as mono-therapy and it is anticipated that amodiaquine as mono-therapy will become increasingly difficult to obtain in the near future.

Chlorproguanil-dapsone (LapDap)

Chlorproguanil-dapsone (CD) was the short-acting drug of choice for this study. Chlorproguanil-dapsone is a non-artemisinin-containing fixed-dose antifolate combination similar to sulphadoxine-pyrimethamine and developed jointly by GlaxoSmithKline (GSK) and WHO/TDR (Tropical

Disease Research) (Lang and Greenwood, 2003). It was briefly registered by the Medicines and Healthcare products Regulatory Agency (MHRA), the regulator in the United Kingdom, but was withdrawn in early 2008 by the manufacturer.

Chlorproguanil and dapsone were combined because they were known to be synergistic in combination and in order to obtain an antifolate combination with a more rapid elimination resulting in a shorter residence time in the body than sulphadoxine-pyrimethamine (Lang and Greenwood, 2003). Chlorproguanil metabolises to chlorcycloguanil, which competes for the active site of dihydrofolate reductase (DHFR) and is also the mode of action of pyrimethamine. Dapsone competes for the active site of dihydropteroate synthetase (DHPS), also the mode of action of sulphadoxine. Chlorproguanil and dapsone have similar half-lives of around 12 and 20 h. The two components of SP have half-lives of around 100 and 200 h, respectively (Winstanley et al., 1997). The new combination was thus considered to exert less selective pressure for drug resistance than SP and hence a lower probability of selecting and spreading resistant parasites (Winstanley et al., 1997, Nzila et al., 2000).

Chlorproguanil-dapsone has been shown to be efficacious in Kenya (Watkins et al., 1988, Sulo et al., 2002) and northern Tanzania (Mutabingwa et al., 2001a, Mutabingwa et al., 2001b). There have been concerns about the life span of Chlorproguanil-dapsone when used because it shares similar genetic mechanisms of resistance as

sulphadoxine-pyrimethamine. It was therefore further developed in combination with artesunate as chlorproguanil-dapsone-artesunate (CDA) by the Medicines for Malaria Venture (MMV), GSK and WHO/TDR.

Chlorproguanil-dapsone was chosen over CDA in our study, because at the time of the design of this study chlorproguanil-dapsone was only available as Lapdap, and CDA was not available, and there was no clinical experience with the combination in the treatment of malaria as it was still at an early phase of development and Phase I trials had just started (Olliaro and Taylor, 2003). It was therefore considered premature to use the combination with artesunate (loose or fixed) in the preventive use of malaria in a very young age group.

Interventions

The drug regimens were as follows:

1. SP_AS3 (DAFRA Pharma, Belgium): one SP paediatric-strength tablet (250 mg sulphadoxine, 12.5 mg pyrimethamine) once on the first day of treatment (followed by a placebo SP tablet on days 2 and 3) and one paediatric artesunate tablet (25 mg) tablet, once daily for 3 days.
2. CD (GlaxoSmithKline, United Kingdom). One paediatric caplet (15 mg chlorproguanil and 18.75 mg of dapsone) once daily for 3 days administered with a placebo for 3 days.
3. AQ3_AS3 (DAFRA Pharma, Belgium): one paediatric amodiaquine tablet (67.5 mg), once daily for 3 days and one paediatric artesunate tablet (25 mg) once daily for 3 days.

4. Placebo (DAFRA Pharma, Belgium). Participants in the placebo arm received 2 placebo tablets co-administered once daily for 3 days.
5. Ferrous-sulphate (2 mg/kg/day) (Laboratory and Allied Ltd., Kenya) was given at the first and second IPTi courses (1 month supply), and 1 month later at the fourth scheduled visit (2 month supply) to the parent/guardian of all study participants for home administration during a 4-month period from approximately 2.5 to 6.5 months of age.

All study drugs were good manufacturing practice certified.

Administration of study drugs

All medications were dispensed as crushed tablets mixed – to increase palatability - with pharmaceutical-grade flavoured syrup (Humco Corporation, Texarkana, Texas, USA) immediately prior to administration in an opaque syringe. The first dose of each course of study drug was administered and supervised at the healthcare unit by a study nurse, subsequent doses of each course were administered and supervised at home by study staff. All children were observed for 30 minutes; if vomiting occurred during that period a repeat dose was administered and supervised at the healthcare unit by a study nurse.

Iron was dispensed in bottles with a dropper device in the neck to facilitate accurate dispensing and with a childproof closure. The parent/guardian was instructed to bring along all the bottles of iron provided at the 14 week and 18 week visits, and compliance with iron therapy was assessed by using a measuring stand to determine the quantity used by the 14 week, 18 week scheduled visits. In addition, a follow-up home-visit was scheduled at 6 ½

months to check iron compliance by which time the iron therapy was should have been completed.

Definition and assessment of adverse events

An adverse event (AE) was defined as any unexpected medical occurrence in a participant who was receiving or had received study drugs. An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drugs. It may or may not have been related to study drug. The intensity of each AE was also defined as belonging to grades 1-3, with 1 being the least severe.

A serious adverse event (SAE) was defined as any unexpected medical occurrence that:

1. results in death,
2. is life-threatening,
3. requires hospitalization or prolongation of existing hospitalization,
4. results in disability/incapacity,
5. Other medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered SAEs. Examples of such events are intensive treatment in one of the study clinics for allergic bronchospasm or convulsions that do not result in hospitalization.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization can be AEs or SAEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is an SAE. When in doubt as to whether "hospitalization" occurred or was necessary, it should be considered an SAE.

NOTE: Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Causality of all adverse events is defined in relation to the administration of study drugs:

Definite (most probable) - Events occurring within a timely manner after administration of the interaction/intervention that are known sequelae of the interaction/intervention & follow a previously documented pattern but for which no other explanation is known. This category applies to those AEs that the investigator believes are incontrovertibly related to the interaction/intervention.

Probable - Any event occurring in a timely manner after administration of the interaction/intervention that follows a known pattern of reaction to the interaction/intervention & for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the interaction/intervention.

Possible - Any event occurring in a timely manner after administration of the interaction/intervention that does not follow a known pattern of reaction & for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unlikely to be related but cannot be ruled out with certainty.

Unlikely - In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the interaction/intervention.

Not related - Any AE for which there is evidence that an alternative aetiology exists or for which no timely relationship exists to the administration of the interaction/intervention & the AE does not follow any previously documented pattern. This category applies to those AEs that, after careful medical consideration, are clearly & incontrovertibly due to causes other than the interaction/intervention.

Unclassifiable (insufficient information) - There is insufficient information about the AE to allow for an assessment of causality.

Table 5: Table for grading severity of adverse events

PARAMETER	GRADE 1	GRADE 2	GRADE 3	SAE
HAEMATOLOGY				(Life Threatening)
Haemoglobin >3 mo to <2 years	7.1-10.9	5.0-7.0	<5.0	Cardiac Failure Secondary to anaemia
Absolute Neutrophil Count (would likely only be measured in child hospitalized for severe illness)	750-1200	400-749	250-399	<250
PARAMETER	GRADE 1	GRADE 2	GRADE 3	SAE
OTHER				
Possible drug Allergy (respiratory symptoms)	None	Mild wheezing	Severe wheezing, respiratory difficulty	Severe urticaria Anaphylaxis, Angioedema
Possible drug Allergy (cutaneous manifestations)	Pruritis without Rash	Pruritic Rash	Mild Urticaria	Severe urticaria Anaphylaxis, Angioedema
Possible Drug Fever (Axillary)		37.5-39	>39.5	Sustained Fever: >39.5, >5 days
Jaundice	None	None	Mild jaundice	Severe jaundice or evidence of fulminant hepatitis
Possible Cutaneous reaction to study drug	Erythema with or without pruritis	Diffuse maculopapular rash, dry desquamation	Vesiculation, ulcers, moist (wet) desquamation of <10% of body surface	Exfoliative dermatitis, Moist (wet) desquamation >10% of body surface; (Diagnosis of Stevens-Johnson or Toxic epidermal necrolysis)
Stomatitis	Mild discomfort	Painful; difficulty swallowing, but able to eat and drink	Painful; unable to swallow solids	Painful; requires IV

NOTE: If any of the above symptoms appeared life-threatening, resulted in hospitalization, resulted in a permanent disability or incapacity, or resulted

in death, the event was classified as a serious adverse event (SAE). All grade 3 or grade 4 AEs, all SAEs, and any other AEs that, in the judgment of the nurse could have been related to the administration of study drug, were reported to, and investigated by the clinical officer (Local Safety Monitor). Note that events categorized as grade 4 above were considered as life threatening, and reported as SAEs, even if hospitalization or death did not occur.

Data management and statistical methods

Data were entered using scan-ready Teleforms® and an optical scanner (Cardiff, Vista, California, USA). Data were checked for internal consistency and out of range values. The modified intention-to-treat (ITT) population included all the participants who received the first course of study drug regardless of whether they received all or part of the interventions. Only those who had received all three doses of IPTi or placebo (per-protocol) were included in these per protocol analyses.

We used Cox regression models to estimate the risk of the first or only episode of clinical malaria during the period starting from the first intervention visit and ending at 1 year of age or at censoring due to withdrawal or death. The protective effect (PE) was estimated as $(1 - \text{hazard ratio}) \times 100\%$. The models' assumption regarding the proportionality of the hazard ratio was analyzed by assessing the interaction between age and effect of treatment with a time-dependent Cox regression model. Kaplan-Meier curves were used to plot the time to event analyses.

Multiple malaria episodes and hospital admissions were assessed using generalised estimating equations Poisson regression models were used to take into account intra-individual variations and to make any adjustments. During the 28 days after treatment was administered for an episode of clinical malaria, participants were considered not at risk for a new episode of malaria, and any positive blood smear during that time period was considered a recrudescence.

Post-dose analysis - 30 days after individual IPTi courses:

The person-time at-risk was calculated from the date of the given IPTi course until 30 days after that date or malaria was diagnosed or the participant exited the study before the 30 days ended, whichever occurred first. A Cox regression model was fitted to estimate the risk of the first or only episode of clinical malaria during the 30 day period. The PE was estimated as $(1 - \text{hazard ratio}) \times 100\%$, adjusted for age and sex.

Post-dose analysis by week after individual IPTi courses:

The first IPTi course was excluded from this analysis because the period of post-treatment prophylaxis overlapped with the second IPTi course treatment. A Lexis expansion (Clayton, 1993) was used to obtain estimates within defined time strata at 7 day intervals after IPTi courses 2 and 3 by fitting a Cox regression model to estimate the time to first or only episode of clinical malaria within each time strata. The estimates were obtained by calculating PEs within each consecutive period of 7 days after each of the

relevant courses of IPTi. Infants were excluded from the analysis for a period of 28 days after each event, i.e. if a child had clinical malaria in the middle of a 7 day time period, it was excluded for the next 4 week-strata until a total of 28 days exclusion period had been reached, after which the infant contributed again to the analysis.

Post-dose analysis – biweekly time-interaction models:

The first IPTi course was excluded from this analysis as well because the period of post-treatment prophylaxis overlapped with the second IPTi course treatment. A Lexis expansion was used to obtain estimates within defined time strata at 14 day intervals after IPTi courses 2 and 3 by fitting a GEE time-interaction Poisson model to take into account intra-individual variations and to make any adjustments. Multiple episodes of clinical malaria were assessed, and PEs calculated as $(1 - \text{incidence rate ratio}) \times 100\%$ within each consecutive period of 14 days after each of the relevant courses of IPTi. Infants were excluded from the analysis for a period of 28 days after each event, i.e. if a child had clinical malaria in the middle of a 14 day time period, it was excluded for the next 4 week-strata until a total of 28 days exclusion period had been reached, after which the infant contributed again to the analysis.

The GEE time-interaction Poisson model analysis was pooled across the respective IPTi courses allowing for a more robust estimation of PEs over time. Biweekly intervals were preferred for analysis because some weekly intervals had very few episodes of clinical malaria or lacked them altogether.

Log-binomial regression models were used to calculate prevalence rate ratios for the 12 month cross-sectional survey. Risk ratios involving count data were calculated using appropriate Poisson regression models.

Nutritional indices were generated using growth references from the National Center for Health Services, USA and the World Health Organization (CDC, 2005). The analysis was done using SAS version 9.1.3 (SAS Institute, Cary, North Carolina, USA), and STATA version 8.2 (STATA corporation, College Station, Texas, USA).

Ethical approval

The study was conducted according to good clinical practice guidelines and monitored by a DSMB. Safety issues were also overseen by the safety panel of the IPTi consortium. The protocol was approved by the National Ethical Review Committee of the Kenya Medical Research Institute (KEMRI) in Nairobi, and the Institutional Review Board of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. The study is registered with ClinicalTrials.gov, identifier NCT00111163.

Chapter 5: Results

Study site preparation

The recruitment of study personnel, their training in GCP and standard operating procedures (SOPs) was completed by February 2004. The trial started in March 2004 after a satisfactory site inspection by a team of investigators. Enrolment of potential study participants commenced at the four study sites within monthly intervals of each other in order to allow for effective logistical coordination (due to remoteness of some sites) and adequate response to community mobilisation. Some of the initial challenges, such as road access to the remote study sites and re-establishment of cold-chain facilities required for safe vaccine storage were overcome with the collaboration and assistance of the Kenyan Ministry of Health, the local administration and community.

The trial profile

Recruitment started in March 2004 and was completed 24 months later in March 2006. One thousand five hundred and sixteen (1516) infants were enrolled over a period of two years. 1365 children were included in the ITT population, defined as all enrolled children who received at least one dose of study drug and had not reported to be ill with clinical malaria on or before their first intervention visit. The distribution of study participants within the four randomization arms was fairly balanced (Figure 15: Trial Profile, Page 101). The remaining children were not included because they no longer

fulfilled the inclusion criteria by the time they were scheduled to receive their first dose of study drug; within the one month period between the first immunization visit when the children were enrolled and the first course of intervention at the second immunization visit, 6 children had died, 41 had migrated outside the study area, 68 had withdrawn from the study, and 32 had developed clinical malaria and received alternative antimalarial medication. An additional 12 children reported sick with clinical malaria on their first intervention visit.

Administration of all three courses of IPTi was completed by December 2006. Over the duration of the entire study (follow-up to 24 months of age), 1983 ITNs were issued to participants, 14596 sick visits were attended to, and 850 hospitalizations were facilitated.

Participant and baseline characteristics

The participant and baseline characteristics of the ITT population as assigned to the four randomisation arms are presented in Table 6 (Page 102). The four study groups were comparable with regard to gender, Hb genotype, G6PD phenotype, weight-for-age, age at first, second, and third IPTi doses, use of ITNs, and loss to follow-up due to deaths (Table 6).

The average age was 2.7 months on enrolment in all 4 groups. About 1 in five children carried the sickle cell trait (Haemoglobin AS) and about 1 in 50 had sickle cell anaemia. G6PD deficiency was present in about 1 in 4 children, half of which was defined as mildly-deficient.

Success rate of follow-up

A fairly high level of compliance was achieved to complete the 12 month follow-up. Of the 1365 children included in the ITT population, 100% received the first course of intervention (by definition of the ITT population), 1317 (96.5%) received the second course of intervention and 1166 (85.4%) received the third course. Furthermore, 55 (4.0%) infants died, 38 (2.8%) withdrew consent, and 191 (14.0%) were lost to follow-up due to migration outside the study area; 1081 (79.2%) completed the 12 month follow-up period (Figure 15: Trial Profile, page 101). 1050 (76.9%) children were included in the per-protocol (PPT) population which was defined as all enrolled children who received all the three courses of the intervention within 28 days of their scheduled visits, had not reported ill on or before their first intervention visit, and stayed within the study area throughout the intervention period. The randomization of one study participant was unblinded due to the recommendation of the Local Safety Monitor and agreement of the DSMB chair, on suspicion of sensitivity to sulphur-based drugs because of a slight rash developed within 30 minutes of study drug administration. The child was withdrawn from receiving any more study drugs but was regularly followed-up and continued to benefit from free healthcare as promised until completion of the study. There was a differential loss to follow-up in the CD3 arm with a slightly higher number of migrations outside the study area within the five month period between the second and third courses of the intervention (Figure 15)

Figure 15: Trial Profile

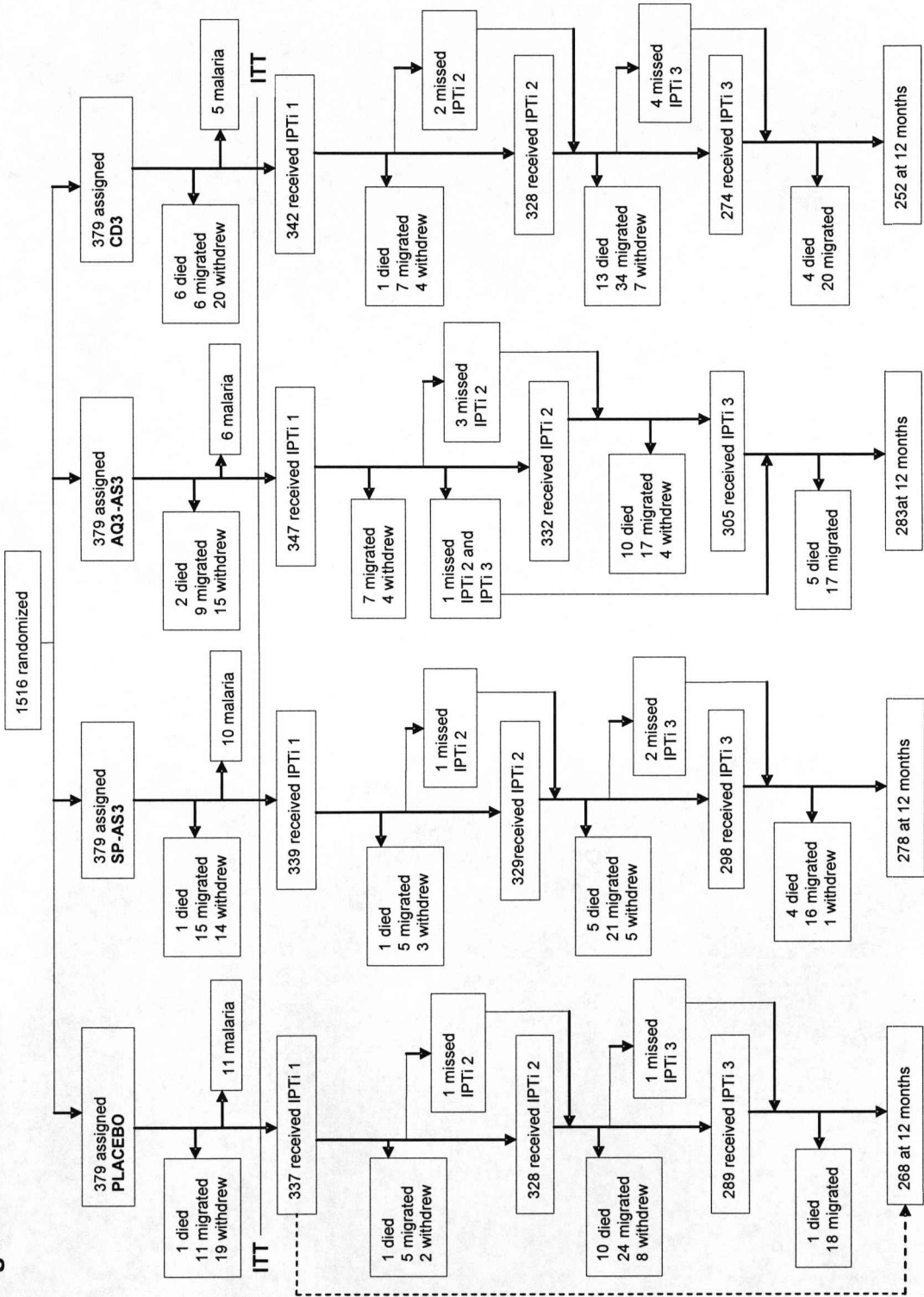


Table 6 Characteristics of IPTi study arms

Parameter	Placebo (n=337)	SP-AS3 (n=339)	AQ3-AS3 (n=347)	CD3 (n=342)
Male sex [%]	46.9	53.1	53.9	50.6
Haemoglobin genotype: †				
AA [%]	75.3	76.1	78.4	76.7
AS “	23.3	22.9	18.9	21.0
SS “	0.4	0.4	0.7	0.4
Other “	1.1	0.7	2.1	2.0
G6PD deficiency:				
Normal [%]	73.9	71.6	68.0	72.2
Mild-deficient “	12.5	15.4	13.3	11.4
Deficient “	13.6	13.0	18.7	16.4
Age at 1 st IPTi [months] (mean± SD)	2.7 ± 0.4	2.7 ± 0.4	2.7 ± 0.5	2.7 ± 0.5
Age at 2 nd IPTi [months] ”	3.7 ± 0.5	3.7 ± 0.5	3.7 ± 0.6	3.7 ± 0.6
Age at 3 rd IPTi [months] “	9.2 ± 0.3	9.2 ± 0.3	9.2 ± 0.3	9.2 ± 0.3
Weight-for-age z score at 1 st IPTi “	0.3 ± 1.1	0.3 ± 1.1	0.3 ± 1.1	0.3 ± 1.1

Note: † At 1 year of age. [%] - figure is presented as a percentage.

(%) – figure in brackets is a percentage.

Protective efficacy (PE)

Intention to treat analysis

Surveillance during the study was conducted by passive case detection in addition to the regularly scheduled visits. The effects of IPTi on malaria and anaemia in the first year of life are shown in Table 7, Page 106.

Clinical malaria

A total of 918 episodes of clinical malaria were detected. The protective efficacy against the primary outcome of this study, i.e. the first or only episode of clinical malaria in the first year of life, was 25.7% (95% CI: 6.3, 41.1; $p=0.012$) in the SP-AS3 arm, 25.9% (95% CI: 6.8, 41.0; $p=0.010$) in the AQ3-AS3 arm, and 16.3% (95% CI: -5.2, 33.5; $p=0.127$) in the CD3 arm when compared to placebo. The median time to the first or only episode of clinical malaria during the first year of life was longer in the SP-AS3 arm (204 days; $p=0.010$) and the AQ3-AS3 arm (208 days; $p=0.007$) when compared to placebo but there was no difference in the CD3 arm (196 days; $p=0.633$) when compared to placebo (196 days).

When multiple episodes of clinical malaria were considered the corresponding protective efficacy results were 22.2% (95% CI: 2.5 , 37.8; $p=0.029$), 24.7% (95% CI: 6.4 , 39.5; $p=0.011$), and 10.5% (95% CI: -11.6 , 28.2; $p=0.324$), for SP-AS3, AQ3-AS3 and CD3 respectively.

A more specific case definition for clinical malaria (with >5000 parasites/ μ L of blood) showed a much higher protective efficacy and yielded the

following corresponding results for the first or only episode analysis 48.9% (95% CI: 12.2 , 70.3; $p=0.015$), 41.2% (95% CI: 2.5 , 64.5; $p=0.040$), and 3.4% (95% CI: -52.3 , 38.8; $p=0.880$) , for SP-AS3, AQ3-AS3 and CD3 respectively. Kaplan Meier survival plots of the above described data are shown in Figure 16, Page 108.

Anaemia

The protective efficacy against the first or only episode of mild anaemia (Hb <11.0g/dL) was 16.4% (95% CI: -0.6 , 30.4; $p=0.057$) in the SP-AS3 arm, 20.3% (95% CI: 4.0 , 33.9; $p=0.017$) in the AQ3-AS3 arm, and 8.0% (95% CI: -10.6 , 23.5; $p=0.375$) in the CD3 arm. The corresponding figures for moderate-to-severe anaemia (Hb <8.0g/dL) were 27.5% (95% CI: -6.9 , 50.8; $p=0.105$), 23.1% (95% CI: -11.9 , 47.2; $p=0.170$), and 11.4% (95% CI: -28.6 , 39.0; $p=0.525$). Kaplan Meier survival plots of the above described data are shown in (Figure 17, Page 109 and Figure 18, Page 110). Multiple episodes of anaemia (incidence density) were not considered because of the long recovery times from malaria associated anaemia, even after effective antimalarial treatment (Price et al., 2001).

Participants, recorded as having had poor iron compliance were 16.7% in the SP-AS3 arm, 17.9% in the AQ3-AS3 arm, 15.8% in the CD3 arm, and 16.0% in the placebo arm.

Sick child visits and hospital admissions

There was no evidence of any effect of the intervention on the frequency of all-cause sick child out-patient visits. None of the IPTi regimens appeared

to provide statistically significant protection against, all-cause hospitalizations, malaria-related hospitalizations, or hospitalizations related to moderate-to-severe anaemia (Table 7).

Per protocol analysis

Of the 1365 enrolled infants, 1050 (76.9%) contributed to the per protocol analysis. The results of the PPT analysis have been presented in Table 8 and are generally consistent with the ITT analysis. The results which achieved statistical significance for the PPT population, but not in the ITT population were the following: protective efficacy against the first or only episode of mild anaemia (Hb <11.0g/dL) in the SP-AS3 arm, 22.6% (95% CI: 4.8 , 37.1; p=0.015); protective efficacy against all-cause outpatient visits in the SP-AS3 arm, 9.4% (95% CI: 2.2 , 16.0; p=0.011), other results came to similar conclusions as the ITT analysis (Table 8, Page 107).

Table 7: Incidences of the main outcomes during the first year of life - ITT

Outcome	Placebo	SP-AS3	AQ3-AS3	CD3
First or only episode of clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 158/161.0; 0.98 Reference	(n=339) 130/176.3; 0.74 25.7 (6.3 , 41.1) 0.012	(n=347) 137/181.4; 0.76 25.9 (6.8 , 41.0) 0.010	(n=342) 136/166.2; 0.82 16.3 (-5.2 , 33.5) 0.127
All episodes of clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 263/197.0; 1.33 Reference	(n=339) 209/201.1; 1.04 22.2 (2.5 , 37.8) 0.029	(n=347) 213/212.0; 1.00 24.7 (6.4 , 39.5) 0.011	(n=342) 233/195.0; 1.20 10.5 (-11.6 , 28.2) 0.324
1st or only episode (>5000 par/μL) Events/PYAR; Rate PE % (95% CI) P-value	(n=346) 38/206.3; 0.18 Reference	(n=350) 20/213.1; 0.09 48.9 (12.2 , 70.3) 0.015	(n=354) 25/219.8; 0.11 41.2 (2.5 , 64.5) 0.040	(n=347) 36/203.0; 0.18 3.4 (-52.3 , 38.8) 0.880
Mild anaemia (Hb<11g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=321) 232/114.8; 2.02 Reference	(n=335) 221/128.9; 1.71 16.4 (-0.6 , 30.4) 0.057	(n=324) 214/127.3; 1.68 20.3 (4.0 , 33.9) 0.017	(n=326) 223/118.5; 1.88 8.0 (-10.6 , 23.5) 0.375
Moderate-to-severe anaemia (Hb<8g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=350) 59/199.3; 0.3 Reference	(n=355) 45/209.5; 0.21 27.5 (-6.9 , 50.8) 0.105	(n=357) 51/213.4; 0.24 23.1 (-11.9 , 47.2) 0.170	(n=351) 52/198.7; 0.26 11.4 (-28.6 , 39.0) 0.525
Out-patient visits Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 1996/210.7; 9.47 Reference	(n=339) 1947/211.1; 9.22 2.6 (-4.9 , 9.7) 0.482	(n=347) 2125/221.5; 9.59 -1.3 (-9.4 , 6.2) 0.746	(n=342) 2051/206.6; 9.93 -4.8 (-13.2 , 2.9) 0.229
All hospitalisations Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 137/210.9; 0.65 Reference	(n=339) 127/211.4; 0.60 7.5 (-19.7 , 28.5) 0.553	(n=347) 147/221.7; 0.66 -2.1 (-32.1 , 21.1) 0.875	(n=342) 130/206.9; 0.63 3.3 (-28.6 , 27.3) 0.818
Hospitalisations - clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 57/210.9; 0.27 Reference	(n=339) 61/211.4; 0.29 -6.8 (-61.5 , 29.4) 0.756	(n=347) 67/221.7; 0.30 -11.8(-67.9 , 25.5) 0.590	(n=342) 58/206.9; 0.28 -3.7 (-60.6 , 33.0) 0.871
Hospitalisations - anaemia (Hb<8g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=337) 44/210.9; 0.21 Reference	(n=339) 41/211.4; 0.19 7.0 (-60.1 , 46.0) 0.793	(n=347) 35/221.7; 0.16 24.3 (-35.2 , 57.6) 0.347	(n=342) 41/206.9; 0.20 5.0 (-64.9 , 45.3) 0.855

Table 8: Incidences of the main outcomes during the first year of life - PPT

Outcome	Placebo	SP-AS3	AQ3-AS3	CD3
First or only episode of clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 132/131.1; 1.01 Reference	(n=264) 99/145.4; 0.68 33.3 (13.5 , 48.6) 0.002	(n=272) 115/149.0; 0.77 26.9 (6.1 , 43.1) 0.014	(n=251) 113/131.7; 0.86 15.4 (-8.8 , 34.2) 0.192
All episodes of clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 217/161.3; 1.35 Reference	(n=264) 156/164.1; 0.95 29.3 (9.2 , 45.1) 0.007	(n=272) 179/175.3; 1.02 24.1 (3.9 , 40.1) 0.022	(n=251) 193/155.6; 1.24 7.8 (-17.0 , 27.4) 0.503
1st or only episode (>5000 par/μL) Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 35/163.8; 0.21 Reference	(n=264) 13/168.5; 0.08 63.7 (31.4 , 80.8) 0.002	(n=272) 20/179.0; 0.11 50.5 (14.3 , 71.5) 0.012	(n=251) 29/160.2; 0.18 16.0 (-37.4 , 48.6) 0.488
Mild anaemia (Hb<11g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=247) 190/90.4; 2.10 Reference	(n=252) 170/102.2; 1.66 22.6 (4.8 , 37.1) 0.015	(n=252) 177/105.1; 1.68 23.9 (6.6 , 38.1) 0.009	(n=239) 179/93.3; 1.92 10.2 (-10.2 , 26.8) 0.303
Moderate-to-severe anaemia (Hb<8g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 43/158.9; 0.27 Reference	(n=264) 34/164.4; 0.21 23.0 (-20.8 , 50.9) 0.255	(n=272) 35/176.6; 0.20 30.8 (-8.2 , 55.7) 0.106	(n=251) 35/156.6; 0.22 17.9 (-28.3 , 47.4) 0.525
Out-patient visits Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 1742/171.8; 10.14 Reference	(n=264) 1577/171.6; 9.98 9.4 (2.2 , 16.0) 0.011	(n=272) 1831/183.5; 9.19 1.6 (-6.4 , 9.0) 0.685	(n=251) 1754/164.9; 10.63 -4.9 (-13.3 , 2.9) 0.227
All hospitalisations Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 107/172.0; 0.62 Reference	(n=264) 89/171.8; 0.52 16.8 (-12.0 , 38.1) 0.226	(n=272) 111/183.7; 0.6 2.9 (-28.2 , 26.4) 0.837	(n=251) 86/165.1; 0.52 16.3 (-16.1 , 39.7) 0.287
Hospitalisations - clinical malaria Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 49/172.0; 0.29 Reference	(n=264) 43/171.8; 0.25 12.2 (-40.0 , 44.9) 0.585	(n=272) 58/183.7; 0.32 -10.8 (-71.3 , 28.3) 0.644	(n=251) 42/165.1; 0.25 10.7 (-45.5 , 45.2) 0.649
Hospitalisations - anaemia (Hb<8g/dL) Events/PYAR; Rate PE % (95% CI) P-value	(n=263) 31/172.0; 0.18 Reference	(n=264) 30/171.8; 0.17 3.2 (-80.3 , 48.0) 0.92	(n=272) 20/183.7; 0.11 39.6 (-22.4 , 70.2) 0.162	(n=251) 24/165.1; 0.15 19.4 (-55.1 , 58.1) 0.519

Figure 16: Kaplan-Meier plots showing the cumulative proportion of children remaining free of clinical malaria episode between the first dose of IPTi and 12 months of age.

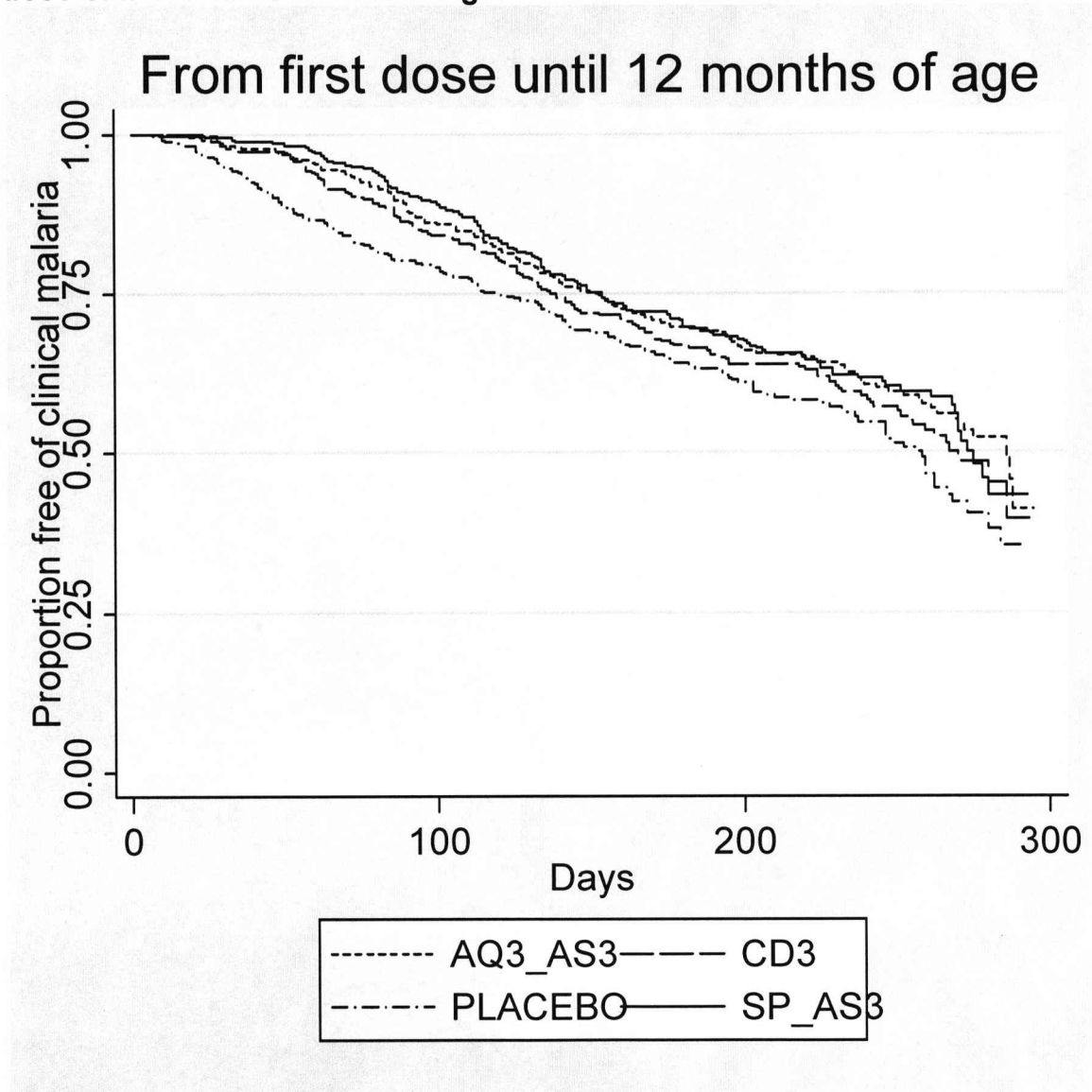


Figure 17: Kaplan-Meier plots showing the cumulative proportion of children remaining free of any anaemia (Hb < 11 g/dL) between the first dose of IPTi and 12 months of age.

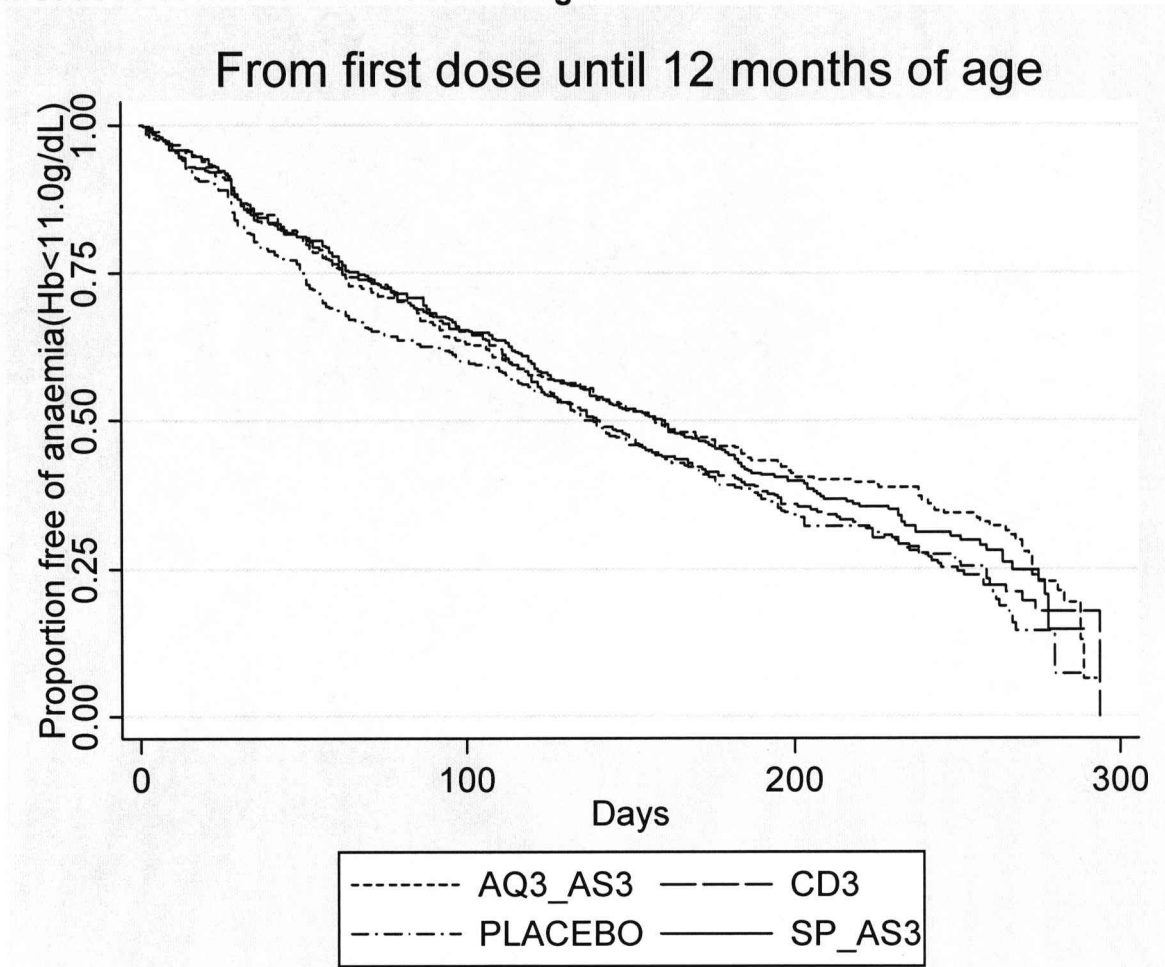
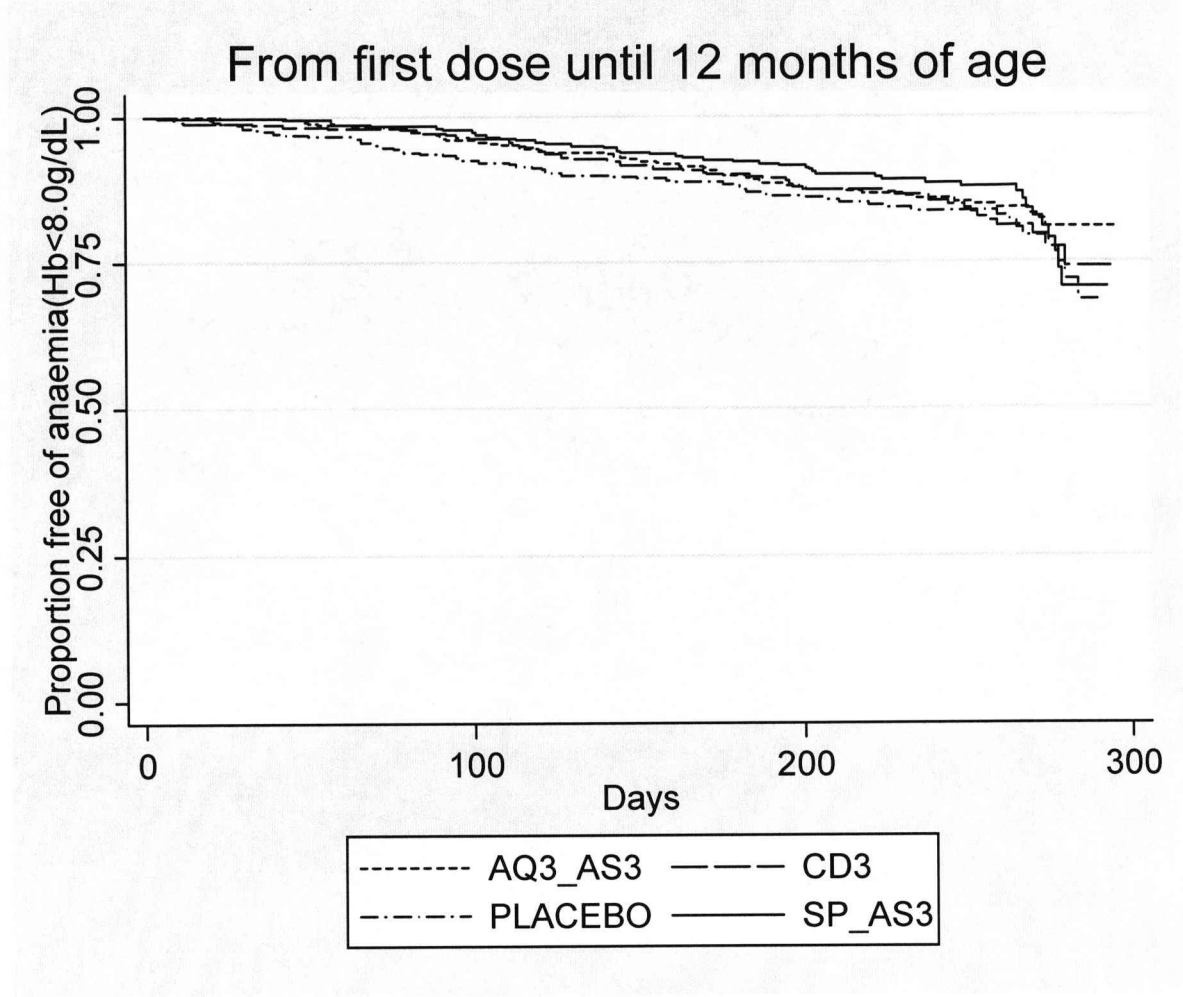


Figure 18: Kaplan-Meier plots showing the cumulative proportion of children remaining free of moderate to severe anaemia (Hb < 8 g/dL) between the first dose of IPTi and 12 months of age.



Post-dose efficacy against malaria

We analyzed the duration of the protective efficacy against clinical malaria with increasing time since each IPTi course using Survival analysis (Cox regression). The models were adjusted for age and sex.

0-30 days

To allow a comparison with previous studies of IPTi with SP, we first estimated the incidence and protective efficacy in the first 30 days after each course (Table 9, Page 117). This showed that the incidence was low after the first course and that the protective efficacy was highest with the sulphadoxine-pyrimethamine, followed by the AQ based regimen and then the CD regimen, as outlined below.

A very high protective efficacy was found against the first or only episode of clinical malaria within a period of 30 days after the first course of IPTi. This was highest at 88.7% (95% CI: 50.9 , 97.4; $p=0.004$) in the SP-AS3 arm, and was 66.6% (95% CI: 15.2 , 86.8; $p=0.021$) in the AQ3-AS3 arm, and 66.1% (95% CI: 14.0 , 86.6; $p=0.023$) in the CD3 arm, respectively.

The corresponding protective efficacies for the 30-days time period after the second course of IPTi were also highest in the sulphadoxine-pyrimethamine arm (89.9% [95% CI: 66.7 , 96.9; $p<0.001$]), followed again by AQ3-AS3 at 72.7% (95% CI: 39.9 , 87.6; $p=0.001$), and 61.7% (95% CI: 22.9 , 81.0; $p=0.007$) with CD3.

By contrast, the protective efficacy for the 30-day time period after the third course of IPTi was much lower in all three interventions groups and was: 32.7% (95% CI: -32.4 , 65.8; $p=0.251$), 38.0% (95% CI: -20.5 , 68.1; $p=0.159$), and 21.7% (95% CI: -52.3 , 59.7; $p=0.471$) in the SP-AS3, AQ3-AS3 and the CD3 arms respectively (Table 9, Page 117).

When the post-dose analyses were conducted for the PPT population the results were similar for the first and second dose, showing greater protective efficacy by 30 days for SP-AS3, followed by AQ3-AS3 and then CD3. However, after the third dose much higher protective efficacy were observed for SP-AS3 and AQ3-AS3 (42.9% and 49.5%) than with the ITT analysis (32.7% and 38.8%), whereas the results for CD4 were lower (Table 10, Page 118).

Protective efficacy by week

The duration of post-treatment prophylaxis was then estimated in more detail by observing the waning protection offered during the second and third courses of IPTi in the first 84 days after each dose. The results from the weekly models represent data from the second and third course only. The first course had to be excluded from this analysis because the maximum possible observation time was limited to 30 days by which time the second course was scheduled to be given. Survival analysis (Cox regression) was used to estimate protective efficacy against the first or only episode of clinical malaria. The observations were made by calculating protective efficacies within each consecutive period of 7 days after each of

the relevant courses of IPTi. Infants were excluded from the analysis for a period of 28 days after each event, i.e. if a child had clinical malaria in the middle of a 7 day time period, it was excluded for the next 4 week-strata until a total of 28 days exclusion period had been reached, after which the infant contributed again to the analysis. Data are presented from the unadjusted models.

0-84 days (IPTi-2 and IPTi-3)

Figure 19 to Figure 24 show the protective efficacy against first-or-only episode of clinical malaria by the week since treatment for IPTi for courses 2 and 3 only. The error bars indicate 95% confidence intervals. The analysis showed that the duration of protective efficacy was longest for the combinations based on sulphadoxine-pyrimethamine and amodiaquine reflecting their longer half-lives compared to CD3.

It also showed that the protective effect declined rapidly from 3 weeks onwards and was no longer evident after 2 months, suggesting that the effect of IPTi occurs only in the immediate period after drug dosing and appears to last as long as the direct pharmacological effect of the drug.

There was evidence of significant protection for at least [4] weeks with SP-AS3 and AQ-AS3, and at least [2] weeks for CD3. Importantly, there was no evidence of a sustained effect of IPTi after this initial period for any of the three drug combinations, neither was there any clear evidence of a rebound within the first 12 months of life.

Figure 19: Weekly PEs post-IPTi 2 for SP-AS3

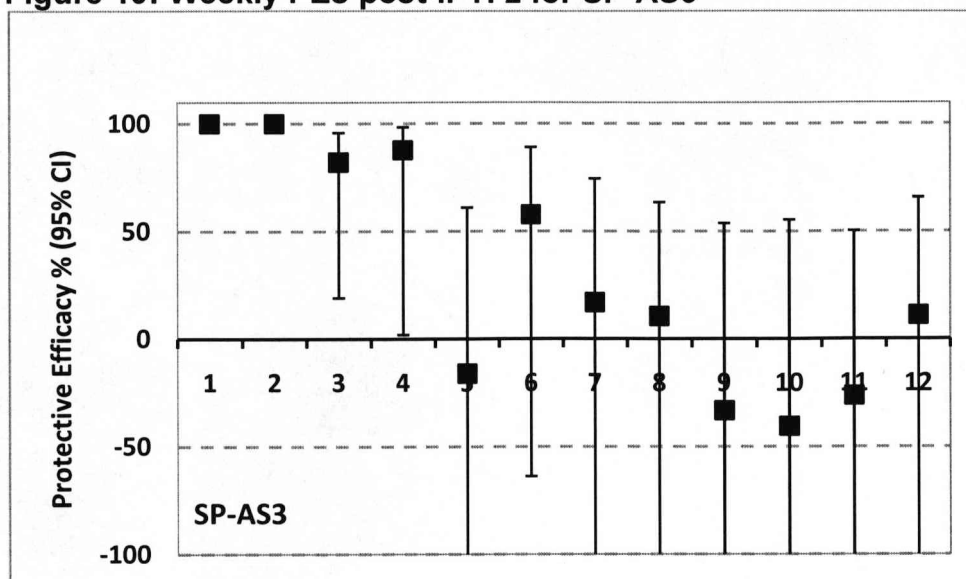


Figure 20: Weekly PEs post-IPTi 2 for AQ3-AS3

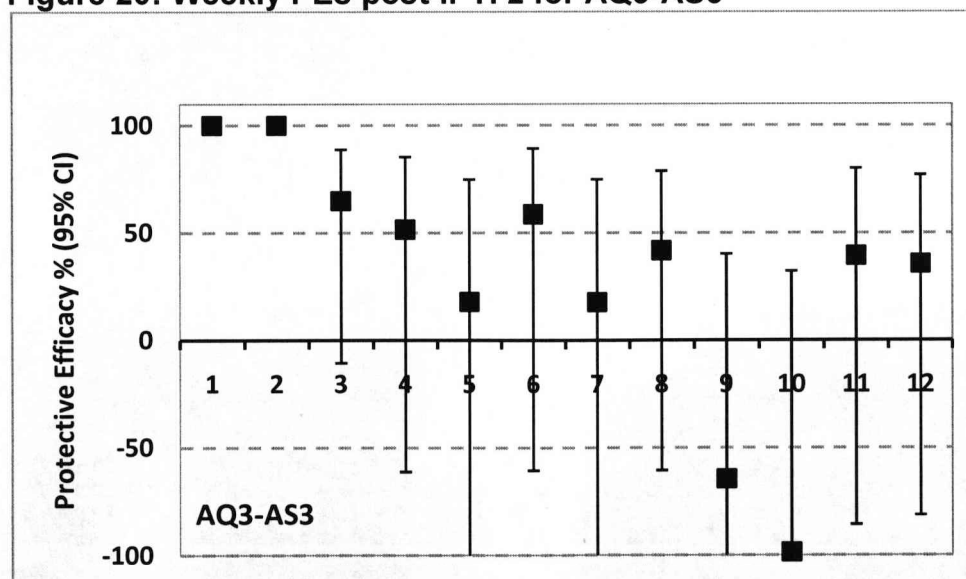


Figure 21: Weekly PEs post-IPTi 2 for CD3

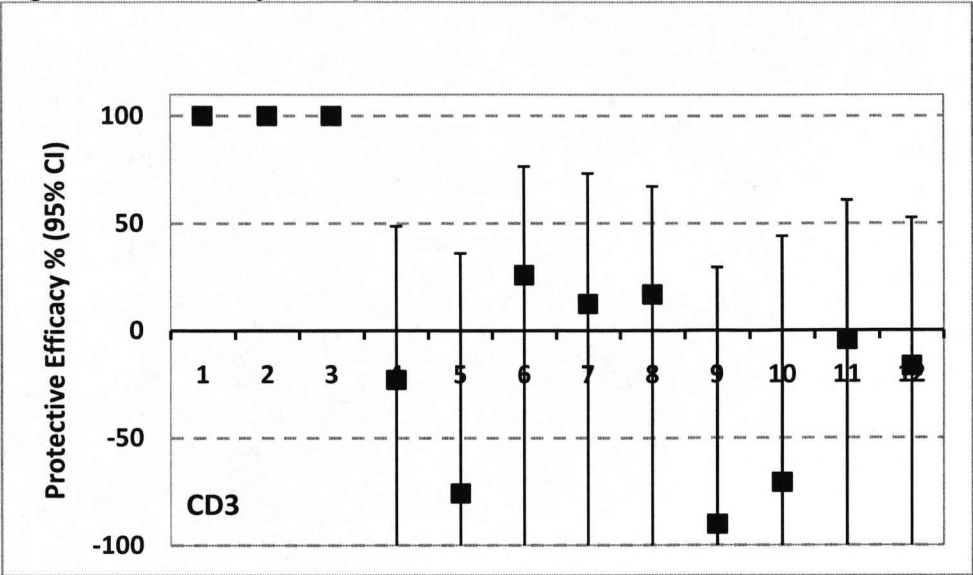


Figure 22: Weekly PEs post-IPTi 3 for SP-AS3

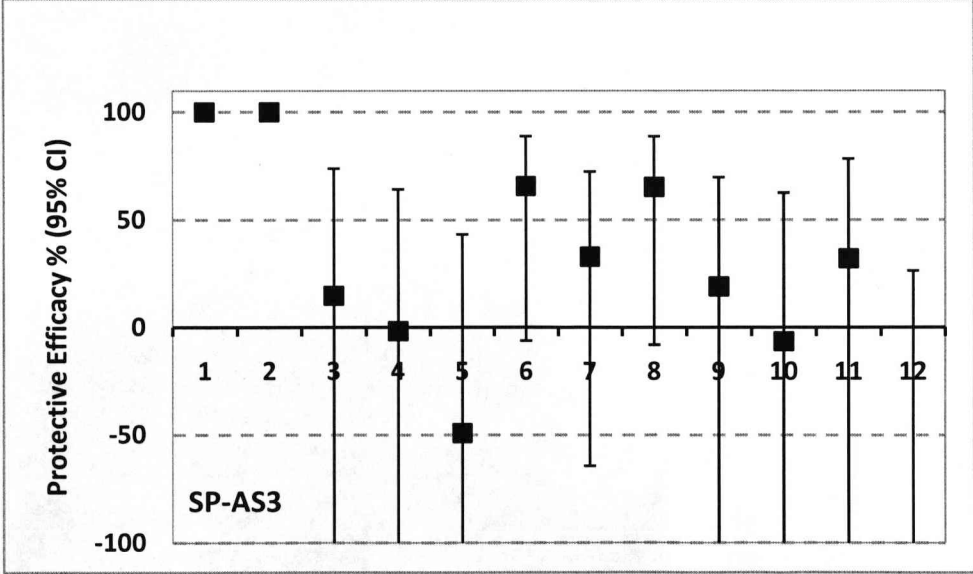


Figure 23: Weekly PEs post-IPTi 3 for AQ3-AS3

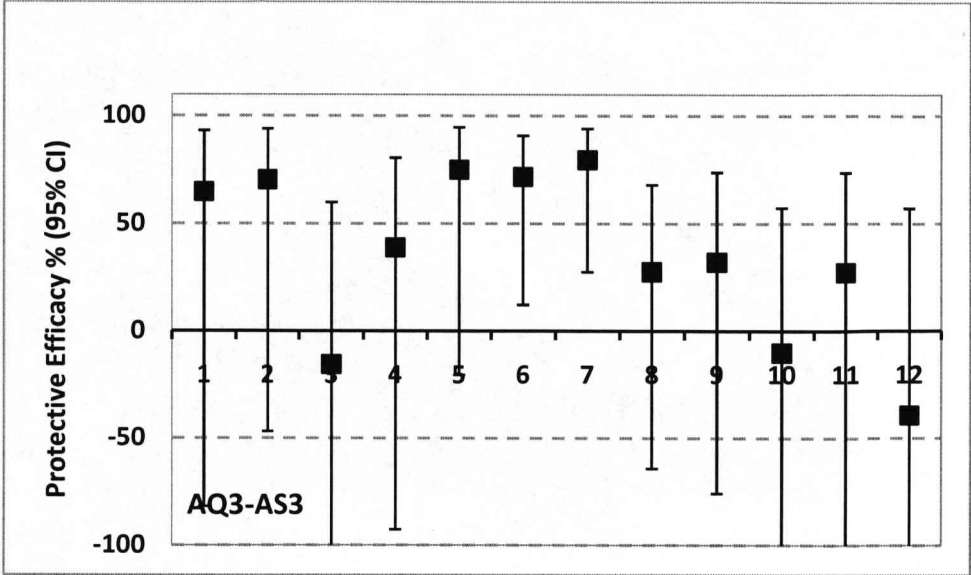


Figure 24: Weekly PEs post-IPTi 3 for CD3

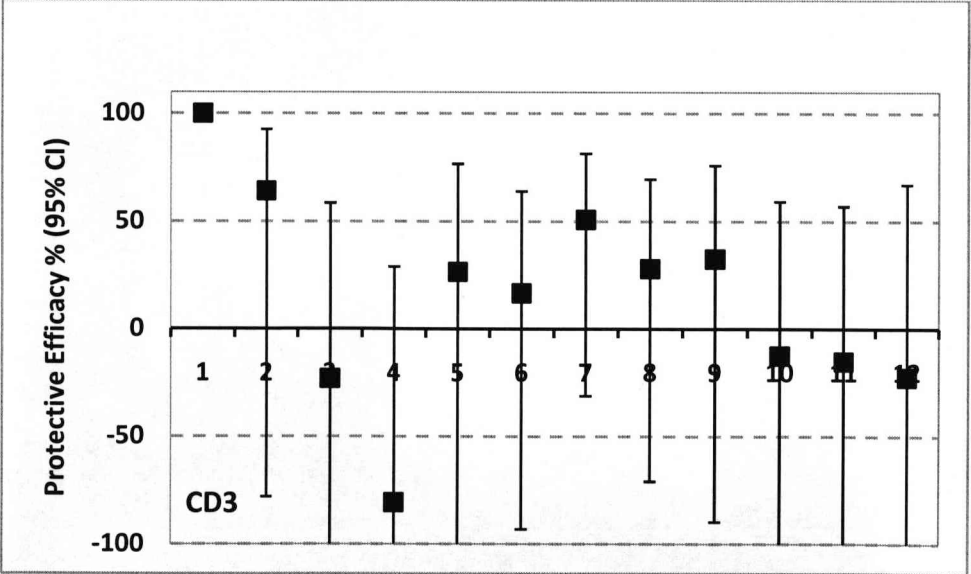


Table 9: Incidences of the primary outcome 30 days after each course of IPTi - ITT

Outcome	Placebo	SP-AS3	AQ3-AS3	CD3
First or only episode of clinical malaria after IPTi-1	(n=337)	(n=339)	(n=347)	(n=342)
Events/PYAR; Rate	17/27.1; 0.63	2/27.8; 0.07	6/28.3; 0.21	6/27.9; 0.22
PE % (95% CI)	Reference	88.7 (50.9 , 97.4)	66.6 (15.2 , 86.8)	66.1 (14.0 , 86.6)
P-value		0.004	0.021	0.023
First or only episode of clinical malaria after IPTi-2	(n=309)	(n=321)	(n=318)	(n=315)
Events/PYAR; Rate	27/24.4; 1.11	3/26.3; 0.11	8/26.0; 0.31	11/25.6; 0.43
PE % (95% CI)	Reference	89.9 (66.7 , 96.9)	72.7 (39.9 , 87.6)	61.7 (22.9 , 81.0)
P-value		<0.001	0.001	0.007
First or only episode of clinical malaria after IPTi-3	(n=187)	(n=213)	(n=235)	(n=184)
Events/PYAR; Rate	19/13.6; 1.4	15/15.9; 0.94	16/18.0; 0.89	16/14.3; 1.12
PE % (95% CI)	Reference	32.7 (-32.4 , 65.8)	38.0 (-20.5 , 68.1)	21.7 (-52.3 , 59.7)
P-value		0.251	0.159	0.471

Table 10: Incidences of the primary outcome 30 days after each course of IPTi - PPT

Outcome	Placebo	SP-AS3	AQ3-AS3	CD3
First or only episode of clinical malaria after IPTi-1	(n=263)	(n=264)	(n=272)	(n=251)
Events/PYAR; Rate	9/21.4; 0.42	1/21.6; 0.05	5/22.3; 0.22	3/20.6; 0.15
PE % (95% CI)	Reference	89.1 (13.8 , 98.6)	46.8 (-58.9 , 82.2)	65.5 (-27.3 , 90.7)
P-value		0.036	0.259	0.11
First or only episode of clinical malaria after IPTi-2	(n=253)	(n=260)	(n=263)	(n=247)
Events/PYAR; Rate	25/19.9; 1.26	2/21.4; 0.09	4/21.5; 0.19	9/20.2; 0.45
PE % (95% CI)	Reference	92.7 (69.1 , 98.3)	85.5 (58.3 , 94.9)	65.0 (25.0 , 83.7)
P-value		<0.001	<0.001	0.007
First or only episode of clinical malaria after IPTi-3	(n=212)	(n=242)	(n=246)	(n=215)
Events/PYAR; Rate	15/17.0; 0.88	10/19.7; 0.51	9/20.0; 0.45	14/17.4; 0.8
PE % (95% CI)	Reference	42.9 (-27.1 , 74.3)	49.5 (-15.4 , 77.9)	9.4 (-87.8 , 56.2)
P-value		0.17	0.105	0.792

Figure 25: Biweekly PEs post-IPTi 2 for SP-AS3

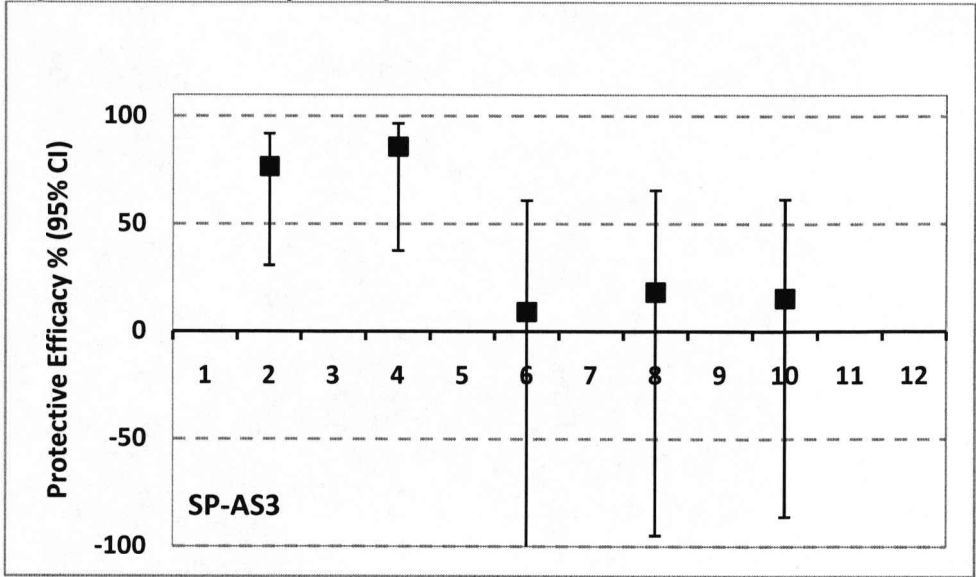


Figure 26: Biweekly PEs post-IPTi 2 for AQ3-AS3

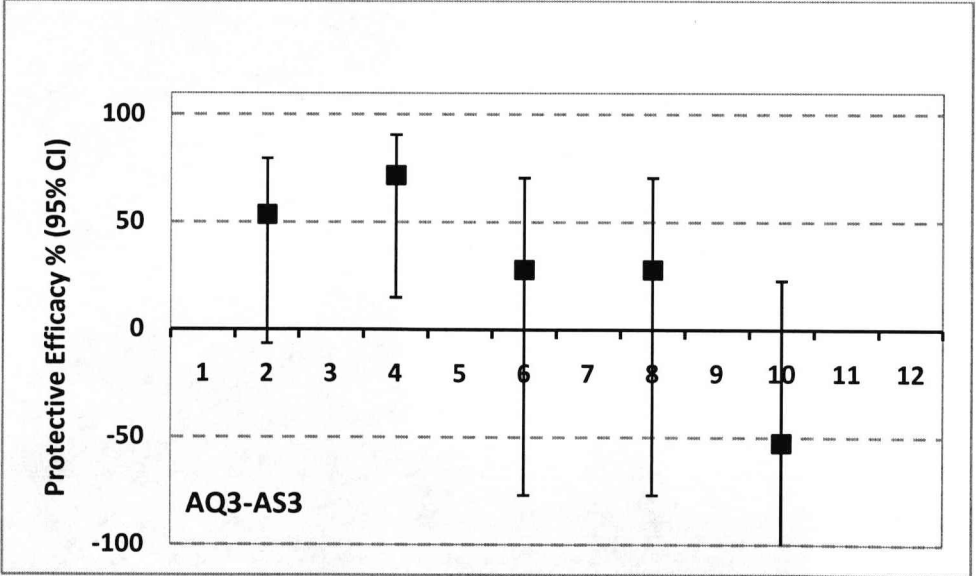


Figure 27: Biweekly PEs post-IPTi 2 for CD3

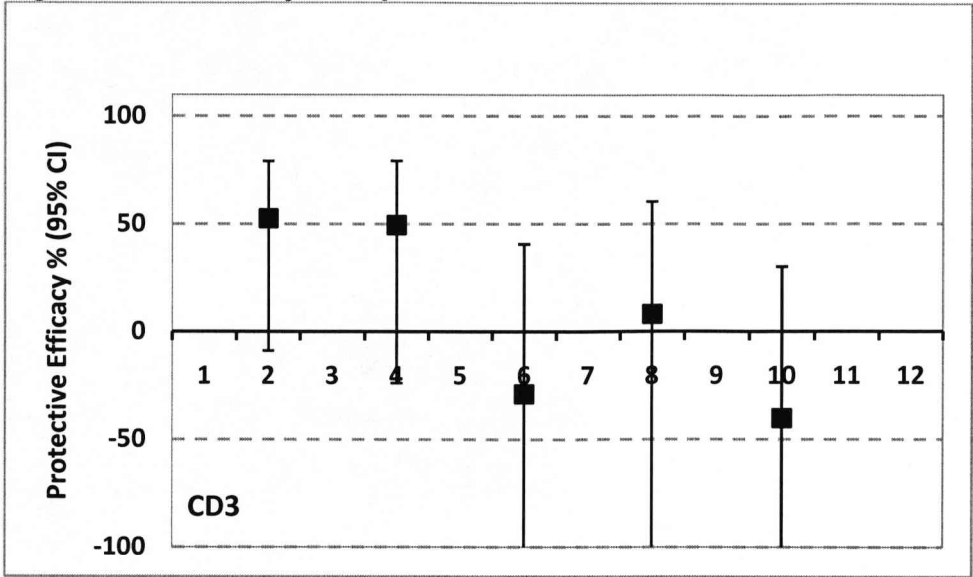


Figure 28: Biweekly PEs post-IPTi 3 for SP-AS3

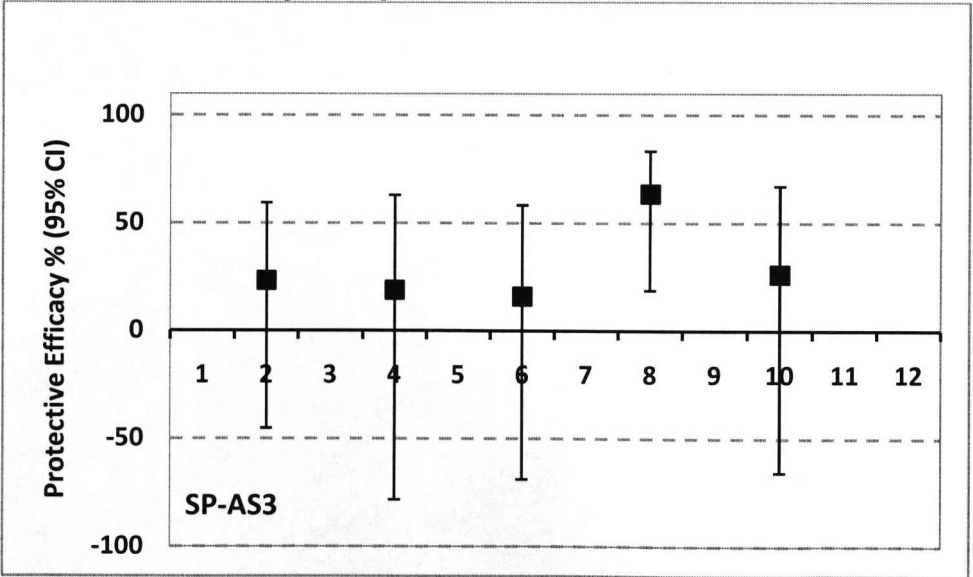


Figure 29: Biweekly PEs post-IPTi 3 for AQ3-AS3

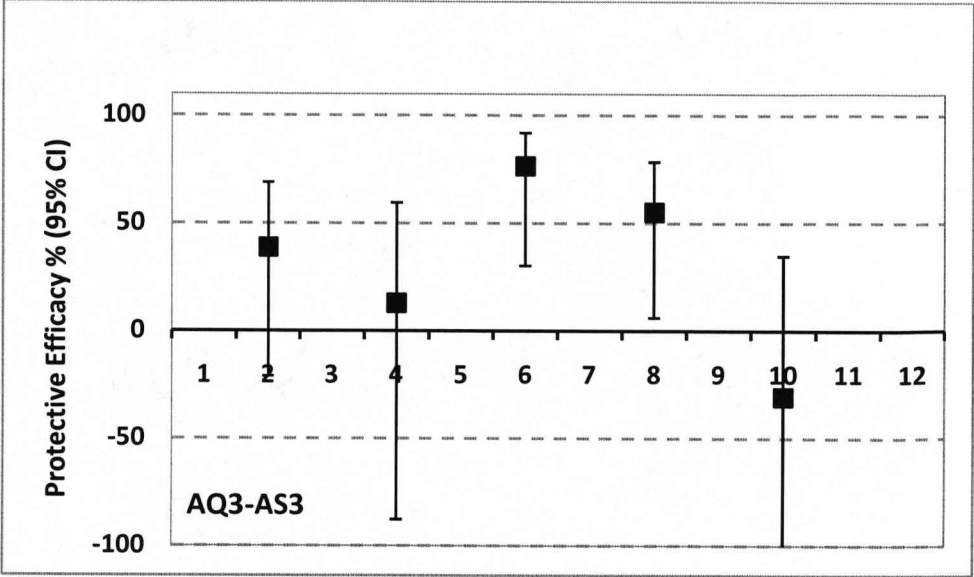


Figure 30: Biweekly PEs post-IPTi 3 for CD3

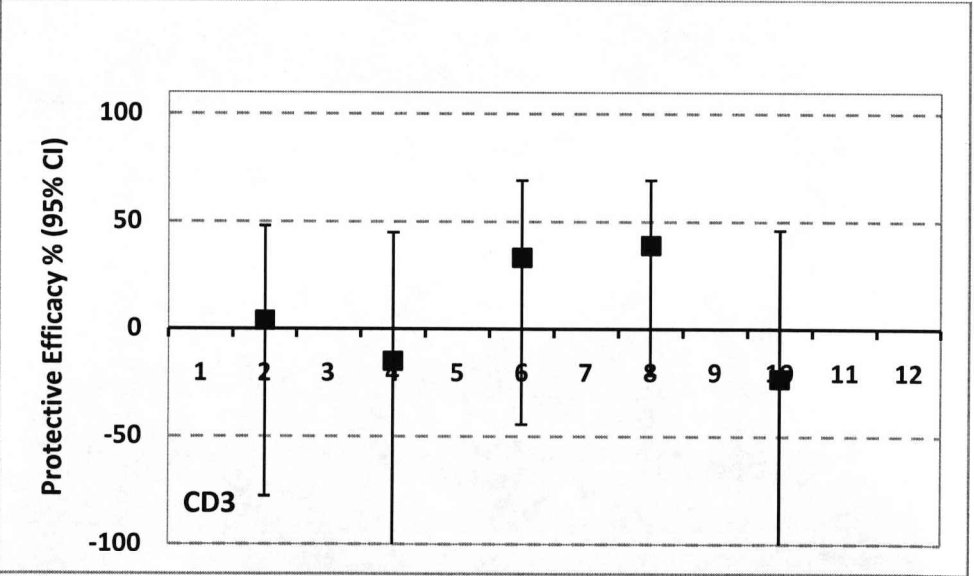


Figure 31: Biweekly PEs pooled post-IPTi 2 and 3 for SP-AS3

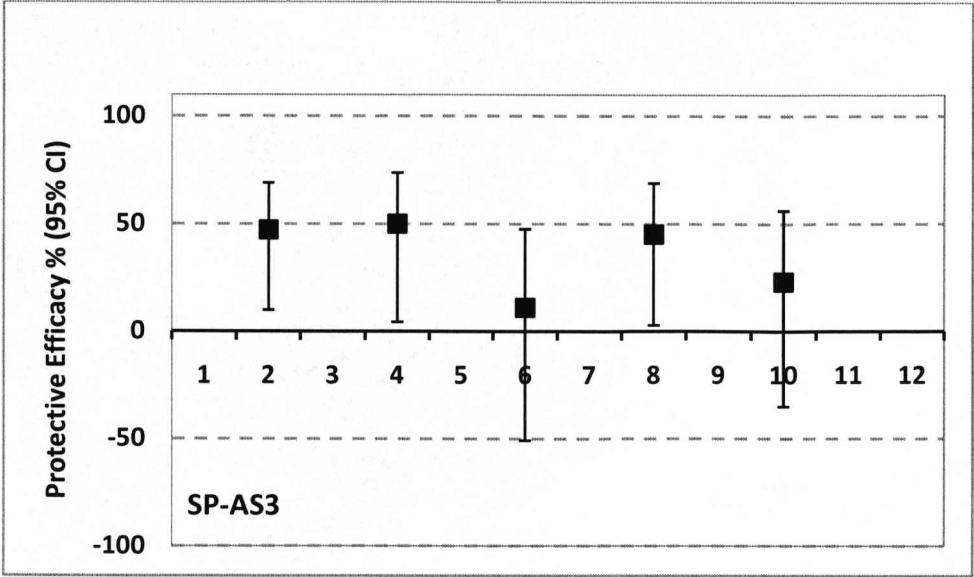


Figure 32: Biweekly PEs pooled post-IPTi 2 and 3 for AQ3-AS3

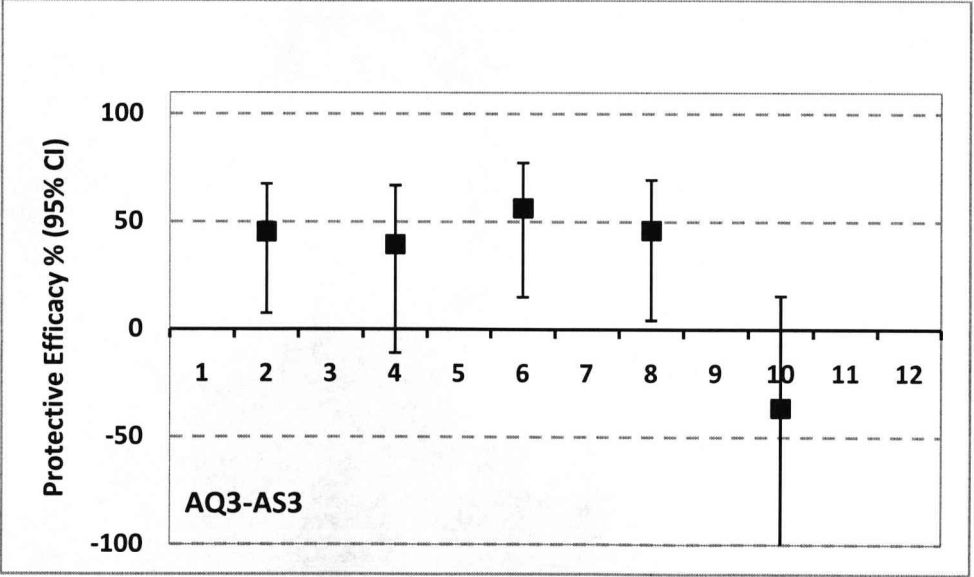
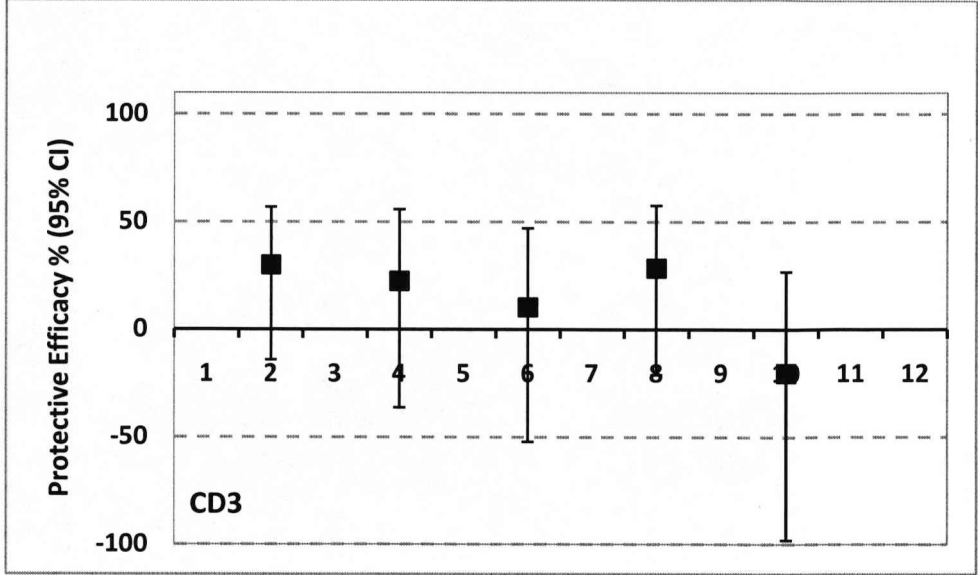


Figure 33: Biweekly PEs pooled post-IPTi 2 and 3 for CD3



Parasitaemia and anaemia at 12 months of age

Children were screened at the age of 12 months to determine the point prevalence of parasitaemia, clinical malaria and anaemia. A total of 1095 of the 1365 children (80.2%) were seen.

The point prevalence at 12 months of age for any parasitaemia was 19.8% in the placebo arm and lower across the 3 intervention arms: 12.4% in the SP-AS3 arm, 11.7% in the AQ3-AS3 arm, and 11.7% in the CD3 arm.

The corresponding figures for clinical malaria were 3.7% in the placebo arm and 5.3%, 4.6%, and 3.9% in the SP-AS3, AQ-AS3, and CD3 arm respectively. None of these differences was statistically significant.

The prevalence of moderate-to-severe anaemia (Hb <8.0g/dL) was low and only 4.8% in the placebo arm. They were slightly lower (not statistically significant) in the intervention arms (1.8%, 3.2%, and 2.7%, respectively) (Table 11, Page 125).

Thus, unlike the effect during the first year as measured by survival analysis, or the protective effect after each treatment course (clinical malaria only) measured by Poisson regression there was no evidence at 12 months that the SP or AQ combinations had a greater or more sustained effect than observed with CD3.

Table 11: Cross-sectional survey at 12 months of age

Prevalence (# at risk)	Placebo (n=273)	SP-AS3 (n=283)	AQ3-AS3 (n=283)	CD3 (n=256)
Parasitaemia (%)	54 (19.8)	35 (12.4)	33 (11.7)	30 (11.7)
PR (95% CI)	Reference	0.63 (0.42 , 0.92)	0.59 (0.4 , 0.88)	0.59 (0.39 , 0.89)
P-value		0.019	0.010	0.013
Clinical malaria (%)	10 (3.7)	15 (5.3)	13 (4.6)	10 (3.9)
PR (95% CI)	Reference	1.45 (0.66 , 3.17)	1.25 (0.56 , 2.81)	1.07 (0.45 , 2.52)
P-value		0.355	0.583	0.884
Anaemia (Hb<8g/dL) (%)	13 (4.8)	5 (1.8)	9 (3.2)	7 (2.7)
PR (95% CI)	Reference	0.37 (0.13 , 1.03)	0.67 (0.29 , 1.54)	0.57 (0.23 , 1.42)
P-value		0.056	0.343	0.229

Rebound analyses

The rebound analyses included all study participants who had taken at least one dose of study drug and were still in the study 30 days after the third course of IPTi. The period under observation was from 30 days after the third course of IPTi until 24 months of age. The results did not show any statistically significant rebound for the first or only episode of clinical malaria, all episodes of clinical malaria, mild anaemia (Hb <11.0g/dL), and moderate-to-severe anaemia (Hb <8.0g/dL). For a more specific case definition of the first or only episode of clinical malaria (with >5000 parasites/μL of blood), the SP-AS3 and AQ3-AS3 arms did not show any

statistically significant rebound but the CD3 arm did, -63.7% (95% CI: -142.5 , -10.5; p=0.014) (Table 12, Page 126).

Table 12: Incidences of some main outcomes between 10 to 24 months of follow-up

Outcome	Placebo	SP-AS3	AQ3-AS3	CD3
First or only episode of clinical malaria	(n=282)	(n=285)	(n=296)	(n=262)
Events/PYAR; Rate	151/200.2;	157/211.4; 0.74	162/210.1; 0.77	147/179.1; 0.82
PE % (95% CI)	0.75	1.5 (-23.1 , 21.2)	-1.1 (-26.3 , 19.0)	-7.3 (-34.6 , 14.5)
p	Reference	0.892	0.920	0.544
All episodes of clinical malaria	(n=283)	(n=286)	(n=297)	(n=262)
Events/PYAR; Rate	456/284; 1.61	464/292.9; 1.58	475/297.4; 1.60	480/256.7; 1.87
PE % (95% CI)	Reference	1.3 (-19.8 , 18.7)	1.0 (-20.8 , 18.1)	-16.5 (-41.2 , 3.9)
P-value		0.892	0.957	0.120
First or only episode with >5000 par/μL	(n=283)	(n=286)	(n=297)	(n=262)
Events/PYAR; Rate	42/288.7; 0.15	47/298.0; 0.16	51/300.3; 0.17	61/255.2; 0.24
PE % (95% CI)	Reference	-8.6 (-64.6 , 28.4)	-16.7 (-75.6 , 22.4)	-63.7(-142.5, -10.5)
P-value		0.699	0.458	0.014
Mild anaemia (Hb<11g/dL)	(n=279)	(n=281)	(n=295)	(n=260)
Events/PYAR; Rate	239/96.7; 2.47	238/105.5; 2.26	254/107.3; 2.37	211/93.7; 2.25
PE % (95% CI)	Reference	8.2 (-9.8 , 23.3)	3.3 (-15.4 , 19.0)	6.5 (-12.5 , 22.3)
P-value		0.349	0.707	0.478
Moderate-to-severe anaemia (Hb<8g/dL)	(n=282)	(n=285)	(n=298)	(n=261)
Events/PYAR; Rate	66/257.5; 0.26	53/268.9; 0.20	62/274.2; 0.23	57/243.6; 0.23
PE % (95% CI)	Reference	22.2 (-11.7 , 45.8)	11.2 (-25.6 , 37.2)	8.0 (-31.1 , 35.5)
P-value		0.173	0.502	0.643

Tolerability

Vomiting is an important factor because it has a tendency to cause complications in the control of malaria in very young infants. All children were therefore observed for a period of 30 minutes; if vomiting occurred during that period a repeat dose was administered and supervised at the healthcare unit by a study nurse.

Out of a total of 11,568 drug doses administered, only 2.1% were vomited. Overall, 4.6% of study subjects experienced at least one vomiting episode (Table 13, Page 129). Those taking study drugs were more likely to vomit than those taking placebo. The total rate of vomiting across the 3 courses was significantly higher with each drug intervention than with placebo: Relative risks in the SP-AS3 arm was 1.8 (95% CI: 1.17 , 2.68; $p=0.007$); in the AQ3-AS3 arm this was 2.1 (95% CI: 1.44 , 3.21; $p<0.001$), and in the CD3 arm 2.4 (95% CI: 1.59 , 3.51; $p<0.001$). Thus, although vomiting was higher than in the placebo group, the three intervention drug combinations were well tolerated by most infants with relatively low rates of vomiting.

Safety and morbidity

There were 593 serious adverse events (SAEs) recorded during the 1st year of life. Of these, 55 were deaths, and 538 were hospitalizations. There was no significant difference in the number of SAEs recorded between the treatment arms and the placebo (Table 14, Page 130). No serious

cutaneous adverse events were recorded. There were no cases of severe haemolysis recorded in any of the study arms. Though, it should be noted that observations were only made from a clinical impression because the study lacked a specific procedure for investigating haemolysis. From further analysis, it was observed that being a G6PD deficient male in the CD3 arm significantly increased ones' chances of having moderate-to-severe anaemia (Hb <8.0g/dL) in the first year of life, -166.8% (95% CI: -497.5 , -19.1; p=0.017). Other G6PD deficiency types (data not shown) did not show any statistically significant association between being in the CD3 arm and having moderate-to-severe anaemia (Hb <8.0g/dL) (Table 15, Page 130).

Table 13: Episodes of vomiting study drug

Dose	Placebo	SP-AS3	AQ3-AS3	CD3
IPTi course 1	(n=337)	(n=338)	(n=348)	(n=342)
Doses administered	1011	1014	1044	1026
Vomit episodes (%)	13 (1.3)	20 (2.0)	26 (2.5)	26 (2.5)
Participants (%)	11 (3.3)	18 (5.3)	24 (6.9)	18 (5.3)
IPTi course 2	(n=328)	(n=328)	(n=333)	(n=329)
Doses administered	984	984	999	987
Vomit episodes (%)	7 (0.7)	18 (1.8)	24 (2.4)	29 (2.9)
Participants (%)	5 (1.5)	13 (4.0)	18 (5.4)	23 (7.0)
IPTi course 3	(n=292)	(n=298)	(n=308)	(n=275)
Doses administered	876	894	924	825
Vomit episodes (%)	13 (1.5)	21 (2.3)	23 (2.5)	22 (2.7)
Participants (%)	9 (3.1)	8 (2.7)	18 (5.8)	12 (4.4)
Total # doses 1,2,3	2871	2892	2967	2838
Vomit episode (%)	33 (1.1)	59 (2.0)	73 (2.5)	77 (2.7)
Participants (%)	25 (2.6)	39 (4.0)	60 (6.1)	53 (5.6)
Rate Ratio*		1.8	2.1	2.4
(95% CI)	Reference	(1.17 , 2.68)	(1.44 , 3.21)	(1.59 , 3.51)
P-value		0.007	<0.001	<0.001

*** Rate ratio of the total number of episodes divided by the number of treatment given in the intervention group relative to that in the placebo group.**

Table 14: Summary of adverse events during the first year of life

Type of AE		Placebo (n=337)	SP-AS3 (n=339)	AQ3-AS3 (n=347)	CD3 (n=342)
Grade 2 or 1 AEs		2	1	1	2
Grade 3 AEs		4	1	1	4
SAEs	Deaths	12	10	15	18
	Hospitalisations	135	128	147	128
All SAEs					
Events/PYAR		147/1533.8	138/1530.3	162/1683.9	146/1549.8
Rate		0.10	0.09	0.10	0.09
RR (95% CI)		Reference	0.94 (0.74 , 1.19)	1.00 (0.79 , 1.27)	0.98 (0.75 , 1.27)
P-value			0.617	0.975	0.896
SAEs possibly related to IPTi		5	6	5	4

Table 15: Association between CD3 and moderate-to-severe anaemia by G6PD status

G6PD status		Placebo (n=263)	CD3 (n=251)
Anaemia (Hb<8g/dL) (%)		43 (16.4)	35 (13.9)
Female	Mild-deficient		
	PE (95% CI)	Reference	-184.2 (-726.0 , 2.2)
	P-value		0.055
	Deficient		
Male	PE (95% CI)	Reference	0.7 (-140.8 , 59.0)
	P-value		0.988
	Mild-deficient		
	PE (95% CI)	Reference	-52.0 (-220.3 , 27.9)
	P-value		0.271
	Deficient		
	PE (95% CI)	Reference	-166.8 (-497.5 , -19.1)
	P-value		0.017

Chapter 6: Discussion

Key findings

We determined the efficacy of short and long acting antimalarials to obtain a better understanding of the mode of action of IPTi in this area with stable perennial malaria transmission, high usage of ITNs (>70%), and a high level of *P. falciparum* resistance to SP. Our results indicate that use of the short-acting antimalarial combination drug, chlorproguanil-dapsone (CD3) provided less protection as IPTi against clinical malaria and anaemia than the two longer acting combinations: SP-AS3 and AQ3-AS3. As expected, episodes of clinical malaria were suppressed for longer with the regimens containing SP and AQ reflecting the longer duration of post-treatment prophylaxis compared to CD3. SP-AS3 and AQ3-AS3 also provided significantly higher protection against clinical malaria with >5000 par/μL of blood. Though, it should be noted that high density malaria was much more uncommon than clinical malaria and occurred (0.18 incidence rate per person year in placebo arm), and despite the high PE, the absolute number of high density infections that can be prevented by IPT is therefore small. We also found a statistically significant protective effect of AQ3-AS3 in the prevention of mild anaemia in the first year of life (PE 20%). The corresponding figure in the SP-AS3 arm was 16% (statistically non-significant). Participants, recorded as having had poor iron compliance were 16.7% in the SP-AS3 arm, 17.9% in the AQ3-AS3 arm, 15.8% in the CD3 arm, and 16.0% in the placebo arm.

Effect of SP-AS3 and comparison with previous SP trials

The IPTi Consortium recently completed the pooled analysis of the six trials with SP. This showed that SP is associated with a 30% reduction in the incidence of clinical malaria in the first year of life, a 37% reduction in hospitalizations of infants with malaria parasitaemia, a 23% reduction in all-cause hospitalisations, and a 15% reduction in the risk of anaemia (IPTi Consortium, 2008).

The results of our study, where we used SP combined with AS3 is remarkably consistent with these summary estimates. The observed protective efficacy against clinical malaria provided by SP-AS3 was 26%; compared to 30% in the pooled analysis with SP alone. This level of protective efficacy against clinical malaria is remarkably consistent across the 6 SP trials and the current trial, despite considerable variation in the SP regimens used in the different trials, and in the degree of background SP resistance and level of ITN use. Macete *et al.* in Mozambique, using a 3, 4, and 9 month schedule reported a reduction in clinical malaria of 22% (Macete *et al.*, 2006). In Ghana, Chandramohan *et al.* administered 4 courses of SP-IPTi at months 3, 4, 9, and 12 and found a protective efficacy against all episodes of malaria of 25% up to 15 months of age (Chandramohan *et al.*, 2005). The two other studies in Ghana, Kobbe *et al.* and Mockenhaupt *et al.*, used a 3, 9, and 15 month schedule and reported 20% (Kobbe *et al.*, 2007) and 23% (Mockenhaupt *et al.*, 2007) protective efficacy against clinical malaria up to 21 and 18 months of age respectively. In Gabon, Grobusch *et al.* administered SP-IPTi at 3, 9, and 15 months and

Chapter 6: Discussion

reported a 22% protective efficacy against clinical malaria up to 18 months of age, although the results did not reach statistical significance (Grobusch et al., 2007b).

The smaller and non-significant effect of SP-AS3 (16%) on anaemia is also consistent with the pooled estimate found in the previous studies (15%). To date, only 2 of the previous 6 IPTi trials with SP have found a significant protective effect against anaemia: the original IPTi trial by Schellenberg et al in Tanzania (50%), and the trial by Grobusch et al in Gabon (22%) (Schellenberg et al., 2001, Mockenhaupt et al., 2007, Grobusch et al., 2007b). Our trial and the SP trial in Tanzania differed from the other 5 previous SP trials in that they provided 4 months of unsupervised daily iron supplementation and they had high coverage levels of ITNs (83% and 68%). However, the Gabon trial which showed a reduction in anaemia did not provide any iron supplementation and ITN coverage was low (5%). The multifactorial nature of paediatric anaemia seems the most likely explanation for the heterogeneity in trial results with regard to protective efficacy against anaemia (Calis et al., 2008).

Effect of AQ3-AS3

Our results suggest that AQ may be a suitable alternative to SP for IPTi. However, as for SP, our results with AQ3-AS3 (PE 26% against clinical malaria) were less dramatic than the 65% protection with amodiaquine alone reported earlier from Tanzania by Massaga et al (Massaga et al., 2003). This Tanzanian trial was quite different in that IPTi administration

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was not linked to EPI and the 3 doses were given 60 days apart, beginning at 12-16 weeks of age. Importantly, we found that AQ3-AS3 was tolerated similarly well as the other IPTi drug combinations used in this trial. Although the acceptance of AQ is sometimes poor among adults and pregnant women being treated for clinical malaria (Tagbor et al., 2006, D'Alessandro and ter Kuile, 2006, Fanello et al., 2006, Rwagacondo et al., 2004), data from our blinded trial does not suggest that tolerability is a problem in infants.

Mechanism of action

Treatment effect and role of artemisinin

The observed differences between long and short-acting drugs suggest that the prophylactic effect is important for the mode of action of IPTi as discussed later. Nevertheless, the 16% reduction against clinical malaria observed with CD3, also suggests some contribution of efficacious clearance of existing infections (although none of the observed effects for CD3 were statistically significant). If the treatment effect provides some, albeit limited, contribution it still remains unclear to what extent the rapidly eliminated artemisinin derivatives added any benefit. Any direct benefit could have resulted from the improved radical cure of existing infections over and above that of SP or AQ mono-therapy. The benefit would be greatest in children with higher density parasitaemias as low density infections are more likely to be cleared successfully even in the presence of mild to moderate resistant infections (Nosten and White, 2007). However, the effect of this is likely to have been very small as few infants reported ill with

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clinical malaria at the time they were scheduled to receive IPTi, only 2-4% were symptomatic (i.e. those most likely to have higher parasite densities and thus to benefit from the added value of artemisinin over that of monotherapy). Thus the main benefit of adding an artemisinin derivative may be the prevention of abuse of monotherapies and the further development of resistance in the population (White, 2005). This needs to be weighed carefully against the added complexity if combination therapy for IPTi results in longer and more complex regimens (e.g. single dose SP vs. 3 days SP-AS3).

The very high PEs in the 30 days after the first 2 courses of SP suggest that concerns about the potential impact of rising resistance of *P falciparum* to SP (when used for prevention) may not yet be evident at the current levels of SP resistance in western Kenya (46% treatment failure by day 28) (Obonyo et al., 2003), suggesting that SP may remain effective for prophylaxis despite clearly reduced efficacy as therapy. Since parasite density is a strong predictor of treatment failure irrespective of background immunity (Nosten and White, 2007), this difference can probably be explained by the differences in parasite densities in symptomatic children with malaria versus children receiving IPTi (Cairns et al., 2008). Given the short half-life of AS, it is unlikely that its addition to SP had substantial impact on its prophylactic protective efficacy against clinical malaria, but it may have contributed to the prevention of recrudescences. Unfortunately, without an SP alone arm, it is not possible to confirm this hypothesis.

Relative efficacy by treatment course

The high PEs observed with SP-AS3 in the 30 days after the first and second courses of IPTi and the lower PEs in the 30 days after the third course are consistent with the findings of the other IPTi studies (Kobbe et al., 2007, Macete et al., 2006). The reason behind the observed reduction in PEs, which occurs after the 5 month period between the second and third courses of IPTi, is not well understood. It may be the result of a complex interplay of a combination of factors including the loss of maternal antibodies, the development of naturally acquired immunity by all children (including the healthy survivors in the placebo group, thereby diminishing any differences between those in the intervention and placebo arms) and limited exposure to malaria parasites (due to protection by high usage of ITNs). An additional explanation is the relatively lower dosage of intervention drugs received by the older at the third course (9 month of age) due to normal physiological age related weight gain between the first and second dose and the last course. The dosage provided was fixed for all three courses and based on age, not body weight, thus the older and heavier children received considerably less drug in mg/kg than children at the first and second course.

Prophylactic effect: duration of post-treatment prophylaxis

A closer look at cumulative PEs calculated every 7 days after each course of IPTi shows that the post-treatment prophylactic effect does not extend beyond 35 to 56 days after receiving SP or AQ. The results are very similar to a more detailed analysis of the duration of protection against clinical

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malaria provided by Cairns et al on the data from Navrongo. These also found that the duration of protective efficacy was short-lived and lasted for 4 to 6 weeks only, reflecting the prophylactic effect of IPTi (the duration varied with the endpoint used in the analysis) (Cairns et al., 2008). Similar to our study, there was no evidence for a sustained effect thereafter (see also below).

Long term efficacy: Sustained protection/ Rebound

Current study

One of the other important questions that this study addressed was the impact of IPTi in the second year of life. We did not show a sustained protective efficacy effect of SP-AS3 or any of the other two interventions against the observed outcomes in the follow-up period starting from 10 to 24 months. We also did not observe any significant increase or rebound in clinical malaria or mild and moderate-to-severe anaemia with either SP-AS3 or AQ3-AS3. These findings are consistent with the pooled analysis of the other SP trials (see below). We did record a statistically significant rebound effect with CD against clinical malaria with >5000 par/ μ L of blood. Though, the rate of high density malaria was higher in the CD arm than in the placebo arm, the rebound observed may be exaggerated due to the unfavourable significant differential loss to follow-up experienced in the CD arm. This loss to follow-up mostly occurred during the extended period between the second and third courses of IPTi and was mainly due to migration outside the study area. Another explanation is that this particular result may have occurred by chance and may reflect the fact that we

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compared multiple secondary endpoints (multiple comparisons), as there was no indication that this occurred for any of the other endpoints measured, or any of the other two interventions used. In addition, given its short half-life and unlikely influence on the acquisition of natural immunity, this unexpected finding may not be a true effect.

Comparison with results from IPTi Consortium:

These results concerning sustained protection for our longer acting combinations containing SP and AQ are consistent with the pooled analysis from the 6 SP trials in the IPTi Consortium, which found no significant rebound in episodes of clinical malaria, anaemia or hospital admissions over a period of 5 months after the IPTi intervention was completed (IPTi Consortium, 2008). Nevertheless, it is noteworthy that three studies in Ghana recorded some rebound, in high density clinical malaria (Navrongo), anaemia (Kumasi), and in severe malaria and severe anaemia (Tamale) (Chandramohan et al., 2005, Kobbe et al., 2007, Mockenhaupt et al., 2007). By Contrast, the initial study in Ifakara, Tanzania recorded a sustained protective effect of 36% against malaria in the second year of life (Schellenberg et al., 2005).

Thus, the remarkable effect of sustained protection well beyond the known pharmacological effect of SP to date has only been observed in the Tanzanian study. This difference with the other IPTi-SP trials has generated much debate. Gosling et al., recently published the results of a modelling study that attempts to offer a plausible explanation. The study uses models

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to show that the high PEs and sustained effect into the second year observed in Tanzania may have been due to a unique combination of the high incidence of malaria at the beginning of the study that declined thereafter and continued to do so over the period of follow-up, and the additive effect of high ITN coverage in driving down malaria transmission, and maternal immunity due to reduced exposure (Gosling et al., 2008). The models studied also predicted the observed lack of rebound as a situation of disappearing rebound parasitaemia in the face of decreasing transmission. It is interesting to note that maternal immunity seemed to be more strongly associated with the outcome of the model than the level of ITN coverage.

It is noteworthy, that IPTi trials which included iron supplementation in their design tended to show some protective effect on the prevalence of anaemia (Schellenberg et al., 2001, Chandramohan et al., 2005). Whereas, the trials which excluded iron supplementation (Macete et al., 2006, Kobbe et al., 2007), with the exception of Gabon (Grobusch et al., 2007b), did not show any protective effect on anaemia. Iron supplementation in malaria endemic areas, in the light of recent findings (Sazawal et al., 2006, Richard et al., 2006), is controversial, and provision of indiscriminate (no screening for iron deficiency) iron supplementation in malaria endemic areas is no longer recommended if children are not also protected from malaria. The decision to provide iron in this study was based on the results of a previous study from this same study site that demonstrated its beneficial effect in children using ITNs (Desai et al., 2003). In our study we also provided ITNs to all

participants, and the trial itself provided a high level of free healthcare that reduced the danger of malaria infection to a minimum.

Since iron was given to all four arms of the study, the observed PE on the prevalence of anaemia is probably due to a true difference between the antimalarial effect of the study drugs (unless there is yet to be a defined drug interaction between iron and either of the antimalarial drugs used).

Drug choices

Adherence to multi-day regimens:

The choice of multi-day regimes in real-life implementation conditions introduces the complication of unsupervised doses and compliance issues. When such a drug is given to “well infants” for prevention rather than treatment, there is probably little motivation for the parent/guardian to comply with the full dosage of a multi-day regimen, particularly if the drug is difficult to administer (e.g. crushing of tablets) and is perceived to be not well tolerated (Sokhna et al., 2008). Reduced compliance is bound to have a negative impact on the efficacy of the drug and the duration of post-treatment prophylaxis and increase chances of the exposure of parasites to sub-therapeutic levels that could encourage further development of resistance. It is possible that crushing adult tablets contributed to making a less palatable drug mixture that may have resulted in increased vomiting in the treatment arms as compared to placebo. At any rate, the level of vomiting is bound to increase with multi-day regimens as compared to a single dose, and this does not augur well for the acceptance of IPTi with

such a drug in the community. Indeed, if not properly addressed, the issue of increased vomiting (such as is common with mefloquine in infants) (Luxemburger et al., 1996) could well have a negative impact on the uptake of EPI vaccines.

The addition of AS:

The interpretation of our study results may be limited by the addition of AS to the two arms that contained the long-acting drugs, but not to the short-acting CD arm. At the time, the inclusion of AS was dictated by the KEMRI National Ethical Review Committee (NERC). The NERC considered SP and AQ as failing drugs in terms of treatment efficacy, and were concerned that study participants in those arms should not be exposed to the risk of failed treatments. It remains unclear if AS confounded the treatment effects of SP and AQ as compared to CD. As it has been shown that SP and AQ are more efficacious with the addition of AS (Obonyo et al., 2003, Adjuik et al., 2002, Doherty et al., 1999), it may be that the PEs observed in the study were in part due to the added benefit of AS. Another complication that could have been introduced by the addition of AS is directly linked to the supposed mode of action of IPTi. If the post-treatment prophylactic effect of a long-acting, but 'failing' drug (due to moderate levels of resistance) results in suppression and thus persistence of low-grade parasitaemia at levels that do not cause harm, it could boost the acquisition of natural immunity, similar to some vaccines. The addition of such an effective treatment component like AS may interfere with this process by rapidly clearing all the parasites.

Other alternatives:

Mefloquine was not selected due to concerns about vomiting rates (based on information from using a 25mg/kg dose) and irritability/restlessness in very young children treated with the drug (Luxemburger et al., 1996, ter Kuile et al., 1995, Slutsker et al., 1990). The Kilimanjaro IPTi study was already planning to study mefloquine.

Currently, another viable alternative may be DHA-piperaquine because it fits the profile of the more efficacious IPTi drugs because of the long half life of piperaquine. It may also be possible to develop a single dose regimen which would make it an ideal candidate for IPTi. Though, if we take the approach of using preventive drugs that are different from the recommended treatment drugs then we may have a dilemma with regard to DHA-piperaquine because it is considered a good candidate for a first-line treatment drug!

SP plus AQ is also a viable drug combination that has been tested for IPTc in a study in Senegal (Sokhna et al., 2008). In areas of Africa where resistance to both SP and AQ is still low, and a different drug is in use as the first line of treatment, SP+AQ3 may prove to be a good alternative because the combination has been found to be safe, efficacious and well tolerated (Sokhna et al., 2008).

Study Limitations

Efficacy vs. effectiveness

The promising results obtained with the multi-day regimens administered under direct supervision in this trial should be interpreted with caution. The gap between efficacy and effectiveness is likely to be greater for IPTi with multi-day drug regimens than for SP, given that we supervised the administration of all study drugs, which would not be feasible if a multi-day regimen were ever adopted for programmatic use as IPTi. Notwithstanding, the fact that all the drugs used were well tolerated, paediatric formulations of the drugs (which were not available for use in this study) would likely have further reduced episodes of vomiting, improved the accuracy of dosages, simplified the process of drug preparation before administration, and generally contributed to greater acceptability of IPTi.

Investigation of the pharmacokinetic properties of the drugs used and their efficacy in parasite clearance was beyond the scope of this study. Another factor which may have affected the outcomes is that we facilitated hospitalization -- generally at the Provincial Hospital -- for all participants. Our conservative approach to hospitalization may have resulted in a dilution of any effect of IPTi on hospitalization rates.

The results of this study can be generalized to other malaria endemic areas with stable malaria transmission, high coverage of ITNS and similar patterns of antimalarial drug resistance.

The design of this study could have benefited from a few improvements.

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The current design randomized children at the first EPI visit, i.e. 1 month before the first study drugs were dispensed (at the second EPI visit), thus some children died in the interim period, were lost to follow-up, or developed clinical malaria requiring treatment. This required us to use a 'modified' ITT analysis. The one month period between recruitment and the first intervention visit could have been excluded, facilitating a simpler and more elegant ITT approach.

Migration was higher than expected and the sample size calculations could have been adjusted for loss to follow-up due to migration which is a significant phenomenon in this rural setting, affecting young parents and by extension the infant population.

We used dosing based on age and provided a single fixed dose in children 2 to 11 month of age (e.g. all children in the SP group received $\frac{1}{2}$ a tablet at each IPTi dose visit regardless of their bodyweight). The World Health Organization also recommends age based dosing using the same fixed dose for 2 to 11 months old infants. Given the rapid growth in infants, this will have resulted in the very young (and thus lighter) infants receiving a significantly higher dose in mg per kg bodyweight than the older (and thus heavier) infants. Our study did not measure drug levels, but it is not unlikely that these variations in dose will have resulted in variations in achieved drug levels, some of which may have been below the minimum inhibitory concentrations. This may have contributed to some of the variations in the 30-day efficacy between the first two IPTi doses and the last dose. A weight

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based regimen would not necessarily have resolved this, even if a paediatric formulation such as dispersible tablets or syrup would have existed, as weight based regimens are also based on 'strata' and limited by the minimum tablet size (e.g. $\frac{1}{4}$ or $\frac{1}{2}$ tablet) or spoon size (e.g. $\frac{1}{2}$ tea-spoon) that would have been practical to give.

Another issue that may have had an impact on results for anaemia was the adoption of set cut-offs for deciding the level of anaemia and consequently adverse events due to low Hb levels. We used a fixed threshold to define anaemia and severe anaemia. This threshold is based on the experience in older children and adults and may not be the optimal definition in young infants, as it may have resulted in some mis-classification in infants due to the physiological changes in Hb levels in early infancy. In healthy children, physiological haemoglobin levels are relatively high at birth, decline rapidly to reach a nadir at 2 month of age, after which they increase gradually until 6 months of age and remain relatively constant thereafter. Thus, the use of age-dependent cut-offs would have correctly determined the thresholds for anaemia in infants. Some of the episodes in the youngest infants aged 2 to 6 months may thus have been classified as anaemia and that may have reflected to the normal (lower) physiological Hb levels at that age. This could have potentially biased the results of our study towards the null in the first 6 month of age (e.g. showing no, or smaller, differences between intervention arms).

Pooled analysis:

In a pooled analysis like described in this thesis for the IPTi studies, data from individual records of each study subject in all the involved studies are pooled together and analyzed to compute a single estimate (individual patient data analysis). This approach has obvious advantages in terms of increased power and sample size but it also has certain pitfalls that need to be taken into account. In the case of the IPTi analysis, these would include differences malaria transmission settings (and ITN use) between the studies, different intervention periods and dosing schedules (both in terms of duration and relation to the mean age of the cohorts), use and timing of iron supplementation, use of active versus passive follow-up of infants, and the background resistance to the intervention drug used. The results of such pooled analysis should thus be interpreted with caution in order to avoid implying effective outcomes where there may be none. In a situation where results from a single study differ markedly (heterogeneity between trials), e.g. Ifakara trial versus the subsequent trials, it would be best to present the results of the pooled analysis excluding that single trial alongside the complete pooled analysis and discussing any differences may allow for a better understanding of the results. Furthermore, it is not uncommon that a first trial that shows a very promising result, such as the IPTi study in Ifakara (Schellenberg et al., 2001) and the initial bednet trial in The Gambia (Alonso et al., 1991b), triggers a 'donor' response resulting in significant targeted funding of a series of subsequent trials to confirm the results. If significant heterogeneity between the first and subsequent trials is observed it may reflect that the first trial was an outlier and that the

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subsequent trials reflect regression toward the 'true' mean effect. Under such conditions, the results of the first trial may importantly affect the summary estimate of the pooled analysis, and it is perhaps best to omit the results of these initial 'index' studies, as the subsequent studies may never have taken place without the first study showing a promising result.

ITN coverage

The high usage of (ITNs) may potentially provide competing or added benefits in reducing clinical malaria and anaemia. It has been suggested that ITN usage may have a synergistic effect with IPTi (if used concurrently), though others have maintained that there would probably be an additive effect (Greenwood, 2007, Gosling et al., 2008). In our study, the effect of ITNs as a potential effect modifier could not be assessed because ITNs were provided to all participants at enrolment. This was done because the benefits of using ITNs had already been conclusively demonstrated in the same study area (Phillips-Howard et al., 2003b). Though, it was not possible to measure the impact of ITNs on IPTi in this study, the suggestion that synergy between high ITN use and IPTi may have resulted in the relatively high PEs observed in the Ifakara trial is likely inaccurate (Menendez et al., 2007b) because we did not observe such an effect under remarkably similar conditions.

Adverse events

There were no significant differences in the number of serious adverse events between any of the arms and the placebo. In particular, there were

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no serious cutaneous reactions, the main adverse reaction of concern with SP, and no cases of severe haemolysis recorded in the CD3 group, including among G6PD deficient male infants (although they were at a significantly increased risk of developing moderate-to-severe anaemia in the first year of life).

Our results regarding the lack of serious cutaneous reactions with SP will need to be interpreted within the limitations of the sample size. The rate of life-threatening cutaneous reactions with SP when given intermittently is a topic of much debate. Overall, over 4,000 infants in the six SP trials included in the meta-analysis conducted by the IPTi Consortium received 12,000 doses of IPTi-SP and there were significantly fewer serious adverse events (19% to 22%) due to hospitalisations in the SP group than in the placebo group (IPTi Consortium, 2008). In the Kumasi study, two deaths were possibly attributed to IPTi, one from the SP group and the other from the placebo group (in this trial all events occurring within 40 days of IPTi were considered to be possibly related). Only two cases of SJS occurred in the SP group in the Kumasi study at 15 months of age and both children fully recovered. There was also one SJS case in the placebo arm considered not related to IPTi, and a dermatological SAE in the placebo group considered related to IPTi (Kobbe et al., 2007).

Implications for the implementation of IPTi in Kenya:

IPTi may be an appropriate strategy for the control of malaria in Kenya in the endemic areas with perennial transmission such as parts of the Kenya

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Coast line and the western region mostly around Lake Victoria. Although, these areas represent about 20% of the entire Kenyan population (after excluding Mombasa and Kisumu; the 2nd and 3rd largest cities in the country, which have more urban and thus lower transmission risk). Other strategies would be more relevant for the remaining parts of Kenya with malaria transmission that lies in arid/semi-arid epidemic prone and highland epidemic prone areas, and low-risk districts.

The implementation of IPTi as one of the tools of an integrated malaria control programme would require careful monitoring and evaluation. It would be necessary to monitor trends of possible increases or decreases of resistance to the IPTi drug with its initial implementation as recommended by the IOM (IOM, 2008). The development of any major increase in the level of resistance to SP should eventually have a negative impact on its efficacy (White, 2005). However the degree of resistance at which this occurs is not yet defined for SP. The difference in the impact of resistance to SP on case management and on preventive strategies such as IPTi is unclear. It is also unclear how best to monitor the impact of SP resistance on IPTi (and IPTp) effectiveness. It is no longer ethical to conduct in vivo studies in symptomatic children (or pregnant women) using SP as the 1st line treatment for case-management changed to ACT several years ago. One option is to conduct nested in- vivo follow-up studies among the recipients of IPTi who happened to be parasitemic (but asymptomatic) at the time they were scheduled to receive IPT. Furthermore, monitoring the presence of certain mutations known to confer resistance as molecular

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markers should be conducted. This requires that we establish a relationship that would link the efficacy of IPTi in prevention of clinical malaria or malaria associated anaemia, to the rate of parasite clearance in infants receiving IPT and to the presence of specific molecular markers in the population. This is not yet clearly understood and requires further study.

Also the effect of wide scale implementation of IPTi with SP on the level of SP resistance in the population is unclear (Schellenberg et al., 2006, O'Meara et al., 2006), although recent data from Ifakara in Tanzania showed that district wide implementation of IPTi with SP (in addition to SP use in pregnant women) did not affect the frequency of genetic markers in the DHFR and DHPS genes that encode resistance to SP (Schellenberg, 2008).

In the face of successful malaria control programmes and decreasing malaria transmission due to other interventions such as successful vector control and case-management with ACTs (Fegan et al., 2007, Noor et al., 2007), a shift may occur in the age spectrum of the disease burden from infants to older children, thereby rendering IPTi as currently designed less irrelevant. So a similar preventive strategy could be used for a wider age range as currently shown in West Africa, e.g. IPTc in infants as well as school going children. Though, exactly when IPTi or IPTc would become irrelevant is a difficult question that is yet to be answered. This is likely to be a moving target! The spectrum of disease relative to transmission intensity

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is like a continuum. Ideally, IPTi should only be seen as one of the strategies in a more integrated approach to malaria control.

Delivery of IPTi via EPI:

Co-delivery of IPTi through EPI clearly has advantages in terms of increasing cost-effectiveness and the greater chances of acceptability. Data from a Tanzanian implementation study confirm the cost –effectiveness of IPTi (Manzi et al., 2008). It has also been shown to be acceptable and without any negative impact on the EPI system (Pool et al., 2006). The trials conducted with SP have demonstrated its safety and lack of interaction with EPI vaccines (Macete et al., 2006). This trial also collected data on the above mentioned issues which will become available soon. The distribution of EPI coverage in Kenya is closely linked with that of healthcare facilities capable of supporting the cold-chain that is so important for the preservation of vaccines.

Evaluation of IPTi with SP by WHO and IOM.

World Health Organization:

One of the main objectives of the IPTi Consortium is to facilitate the translation of research into policy within the shortest time possible if IPTi is found to be safe, efficacious and cost-effective. In October 2007, a technical expert group meeting (TEG) of WHO was convened in Geneva to discuss the findings presented by the IPTi Consortium at that time. The WHO TEG was presented with both published and unpublished data

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covering a wide range of issues around IPTi-SP. After reviewing the evidence provided, the WHO TEG noted: that alternative, feasible delivery strategies may have to be evaluated in areas with highly seasonal malaria transmission patterns or where EPI coverage is relatively low; that though SP has advantageous properties (inexpensive, single-dose and long-acting) that make it a pragmatic choice for IPTi, there was insufficient evidence to show how the duration of protective efficacy would change with time given the rising rate of resistance to SP; that the optimal dosage of SP for children remained uncertain and there was lack of information on the therapeutic efficacy or pharmacokinetics of SP in parasitemic infants; and that there were only two published IPT trials (at that time) that had evaluated alternative drugs to SP alone (WHO TEG, 2007). Therefore, the WHO TEG concluded that it was premature for it to comment on the relative advantage of SP for IPTi and opted to review further information that was to be availed in 2008 including on other antimalarials (the findings of the study reported in this thesis among others) (WHO TEG, 2007).

United States Institute of Medicine (IOM)

In June 2008, the United States Institute of Medicine (IOM) convened an expert committee, at the request of the Bill and Melinda Gates foundation, in order to evaluate the evidence concerning IPTi-SP and to provide guidance of its value as a continued investment for the Gates foundation (IOM, 2008). The IOM expert committee had access to a more comprehensive dossier of evidence collected by the IPTi Consortium including more published data from the six IPTi-SP trials and unpublished

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data from the trial described in this thesis. The IOM committee evaluated the evidence presented and was satisfied that the pooled analyses were carried out appropriately, though the committee noted that some information on the quality assurance of study-level data and analyses included in the pooled analyses was lacking. The committee supported the notion that IPTi-SP was ready to move to the next level (on condition that the independent technical audit verified the accuracy of the presented evidence) (IOM, 2008). The committee concluded that if the decision were to be made to begin programmatic implementation, then it would recommend that IPTi-SP initially be implemented in perennial, high- or moderate-intensity transmission areas of sub-Saharan Africa where the burden of malaria is high in infancy and resistance to SP is relatively low, in order to maximise the public health impact (IOM, 2008). It also recommended that public health authorities should monitor trends of possible increases or decreases of resistance to SP wherever IPTi-SP was implemented and that the monitoring efforts would be better carried out together with initial implementation in certain districts and countries to gather evidence that would help the development of pragmatic guidelines for larger-scale implementation (IOM, 2008).

Policy Implications

IPTi with SP

Given these positive results of the evaluation conducted by the IOM expert committee and the large implementation trials currently being undertaken by the IPTi Consortium in southern Tanzania involving 12,000 children per

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year, and by UNICEF in six African countries (Benin, Mali, Senegal, Ghana, Malawi, Madagascar) involving 317,000 children per year, it is possible that some countries may consider adopting IPTi-SP as policy. If this were to become a reality, then the most likely beneficiaries in the early stages of programmatic implementation would probably be countries or regions in West Africa, with high to moderate malaria transmission, where resistance to SP is still low and the first-line drug for malaria treatment is not SP. A different strategy of delivery would have to be designed for the areas with highly seasonal transmission.

In these regions with moderate SP resistance, SP should best be reserved for IPT strategies (IPTi, IPTp and perhaps IPTc) and not used as part of the first line combination therapies. In fact, this is currently happening in most countries for IPTp, as almost all countries in Africa currently recommend the use of either AQ-AS or artemether-lumefantrine. None are recommending SP plus artesunate. Under such conditions, the decreasing use of SP for malaria treatment and in turn reduced drug pressure may lessen the threat of rising resistance to SP and allow its effective use for prophylaxis.

SP resistance and alternative antimalarials

Countries or regions with high levels of SP resistance may consider the immediate implementation of IPTi with alternative drugs or drug combinations to SP alone and eventually re-consider if sensitivity to SP were to increase given the increasing use of ACTs at the expense of SP

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monotherapy. Our findings suggest that AQ3-AS3 and SP-AS3 are similarly safe and efficacious and AQ3-AS3 could thus be used as suitable alternatives to SP for IPTi. However, as pointed out earlier in this discussion, the three-day regimen introduces a practical complication in terms of supervised drug administration that may have an impact on cost of delivery and worries over compliance with the full regimen (Kachur et al., 2004).

As for CD, it is too short-acting, not suitable and furthermore, is no longer available as the manufacturer ceased its production. Other alternative drugs with potential for use as IPTi include: mefloquine (MQ) which is currently under investigation by another Consortium IPTi trial in Kilimanjaro, Tanzania; and dihydroartemisinin-piperaquine (DHA-PIP) which so far has not been tested for use as IPTi. Both MQ and DHA-PIP are long-acting drugs that according to our findings may be suitable for use as IPTi if found to be safe and efficacious.

IPTi and integrated malaria control

IPTi may become a useful tool in the integrated malaria control strategy of relevant countries in which the infant populations would stand to benefit from such an intervention (i.e. relatively intense transmission that places the burden on infants). As it becomes more and more obvious that no one single intervention is likely to eliminate the threat of malaria in sub-Saharan Africa and elsewhere (except for, maybe a cheap, abundantly available and highly effective vaccine), IPTi with the appropriate drug choice should be

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considered for implementation alongside other control measures such as vector control including ITNs and IRS. Such programmatic implementations should be carefully monitored and data gathered for preparing guidelines to aid further large-scale implementation (IOM, 2008).

Due to the current increased level of interest in malaria control and its elimination shown by the international community, including some funding agencies, there is renewed optimism among public health practitioners that great strides may be achieved against malaria in the near future. In the event that the UN's vision of an immediate massive up-scaling of LLITN coverage and the use of IRS in all malaria endemic areas actually becomes a reality, leading to the marked reduction in deaths from malaria by 2010 (BBC, 2008), it would be important to monitor the decreasing transmission, incidence rates and inevitable age-shift of the burden of disease beyond infants, in order to identify the appropriate target population for IPTi.

It may well be possible that with successful vector control and the widespread use of ACTs, IPTi may no longer be needed or be cost-effective in the near future (e.g. 5 years). The current study and the previous analysis by Cairns et al (Cairns et al., 2008) suggest that the effect of IPTi is relatively short-lived (4 to 6 weeks). The relative impact will thus depend on the level of malaria transmission. It will thus be important to carefully monitor the role of the different IPT strategies (IPTi,p,c,s) over time when transmission hopefully decreases due to successful integrated control. However, until such successful programs are in place, it makes

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sense to employ IPTi in areas with intense transmissions as one of the effective tools currently available to fight malaria, in order to stem the tide of unacceptable deaths due to this treatable and preventable disease.

Chapter 7: Conclusions and recommendations

This study was conducted under the auspices of the IPTi Consortium from March 2004 to March 2008, and was one of the first IPTi proof of concept trials to investigate the mode of action of IPTi using long and short-acting drug combinations. In conclusion, our results suggest that long-acting regimens are more suitable for IPTi than short-acting regimens in areas of perennial malaria transmission and high ITN coverage. These data also provide a strong indication that the post-treatment prophylactic effect of a long-acting drug provides the bulk of the protective effect of IPTi. There was no evidence for a sustained effect of IPTi beyond the direct pharmacological effect provided by protective drug levels with any of the drug combinations tested, suggesting that these IPTi regimens did not boost the development of protective immune responses in infants. Neither did they increase the risk of malaria or anaemia due to potential rebound malaria once the immediate protective effects of the drugs had waned.

The observed difference between the effect of long versus short-acting combinations is also relevant for other IPT strategies such as IPT in pregnancy (IPTp) and IPT in children (IPTc). These results contribute to efforts to develop a target product profile for alternative drugs to be used for IPT, which is one of the aims of the IPTi Consortium. There is a pressing need to investigate the potential gap between efficacy and effectiveness for multi-day regimens, to test other long-acting combinations (potentially with

paired long-acting antimalarials such as SP plus AQ) and to examine whether the artesunate component of these regimens is of any additional benefit to justify inclusion in preventive strategies that appear to rely primarily on a chemo-prophylactic effect.

For future IPTi studies or implementation programmes, we would recommend the following:

1. If conducted in rural areas; that the design is appropriately adjusted to account for the existing patterns of migration.
2. That the design avoids any significant period between the enrolment of study participants and the commencement of the intervention.
3. That a paediatric formulation of the given drug or drug combination be used, rather than crushing a proportion of adult tablets.
4. That more accurate dosing regimens be developed, probably by better understanding of the pharmacokinetic properties of the given drug.
5. That a rigorous investigation of the effectiveness of multi-day regimens be carried out in a real-life implementation setting.
6. That the added benefit of IPTi as one of several tools employed in an integrated malaria control programme be evaluated.
7. That SP could be reserved for IPT strategies (IPTi and IPTp)

Finally, on the strength of the results of this study and others mentioned in the text, the author is convinced that IPTi, despite its imperfections and drug-choice issues, may become one more useful tool for the prevention of malaria morbidity. A recent commentary in the *Lancet* suggests that others

share this view (Editorial, 2008). However, the current uncertainties surrounding the IPTi strategy need to be addressed (White, 2008b), and more evidence provided from ongoing studies and future studies with more suitable alternative drugs.

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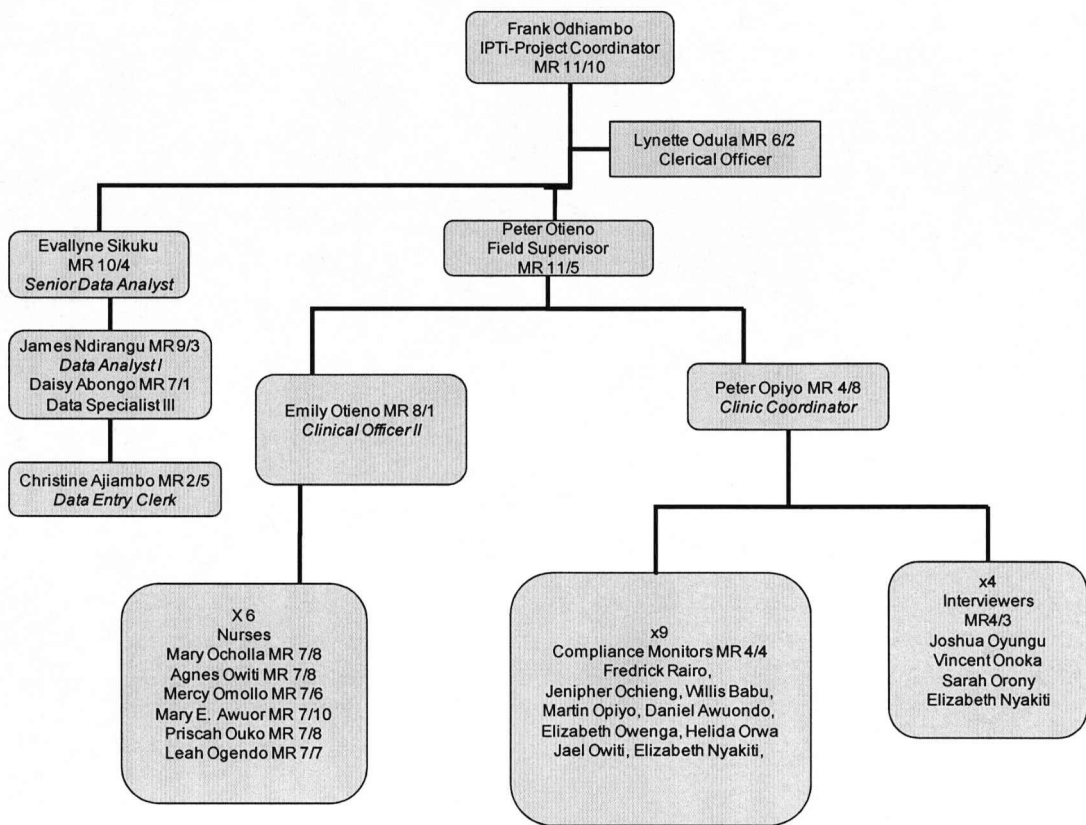
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Appendix I Organogram Field Work



Appendix II Study Forms

Flesch-Kincaid Reading Score: 8.1

Parental/Guardian Permission form – Malaria and Anemia Prevention Study

(IPTi)

Background: The Kenya Medical Research Institute (KEMRI) and the Centers for Disease Control and Prevention, USA (CDC) are doing a research study to find the best prevention for lack of blood (anemia) and malaria. As part of this study we want to compare different ways to prevent lack of blood and malaria. One drug we are giving children is iron. The other drugs are Fansidar® with artesunate, amodiaquine with artesunate, and Lapdap®. All three of these drug regimens are used to treat malaria. You can buy iron, amodiaquine, and Fansidar in many shops in Asembo. Artesunate and Lapdap are not widely sold. We want to know if Fansidar + artesunate, amodiaquine + artesunate, or Lapdap, when given with iron, is better than iron alone for preventing lack of blood in infants. We also would like to know if these drugs change the way the body responds to vaccines. About 1500 infants will be enrolled in the study.

Treatment groups: As part of this study, all children who join the study will receive treatment with iron for 4 months. Children will also receive one of four different types of pills. One group of children will get a crushed sugar pill with no medicine (placebo). One group will get Fansidar + artesunate. One group will get amodiaquine + artesunate. One group will get Lapdap. Children in each of the groups will receive crushed pills in syrup at 10 weeks of age, 14 weeks of age, and 9 months of age. Some pills will be taken in clinic, with another dose the next day and a third dose the day after that. Someone will come to your house to give the drug on the second and third day. Neither the study team nor you can pick the treatment group as this could affect the study results. The treatment will be chosen at random (like flipping a coin). Neither the study team nor you will know which of the drugs your child is receiving until the study is over.

Follow-up Visits: As part of this study, you will bring your child to this clinic a total of 7 additional times during the study (at 10, 14 & 18 weeks, and at 9, 12, 18 and 24 months of age). At each visit a health worker will ask questions about your child's health and examine the child. At some visits, the study staff will take the weight and height of the child. At some visits, she will also prick your child's heel or finger to obtain a blood sample. At some visits, your child will be given the study drug. Each visit should take about 30 minutes.

Study drugs: At the 10-week, 14-week, and 9-month vaccine visit, your child will get medication to take in clinic. A study team member will visit your house the next two days to give the 2 other doses of medicine. Each time your child is given a study drug, our study staff will watch the child for 30 minutes to make sure he does not vomit the drug or become ill. You will also get a bottle with medicine (iron) at 10 weeks, and again at 14 & 18 weeks. We would like you to

give this medicine to your child every day. When your child is 6 months old, we will visit your house to check to see if your child has been given all the iron.

Blood samples: We will prick your child's heel or finger to obtain a blood sample today, and again at 10 weeks, 18 weeks, 9 months and 12 months of age. The amount of blood we will take is small, about ¼ of a teaspoon. The blood will be stored. Some of the blood will be used to see whether your child had an adequate response to the vaccines. Some of the blood will be used to test for a condition in the blood called sickle cell. You will be informed if your child has sickle cell disease. We will provide counseling to help you understand how to seek medical care for your child and how to care for your child at home. Some of the blood will be used to test for other traits that may cause anemia in children, such as G6PD deficiency.

At the 10 week and 12 month visits, we will put a few drops of your child's blood onto a small piece of paper. We will test the blood on this paper to learn more about how well the drugs that are used to treat malaria are working in your community.

At 12, 18 and 24 months, we will take 5 drops of blood to check if your child has malaria and/or anemia (lack of blood). We will provide treatment if your child has anemia or malaria and a history of hot body at these visits.

Nasal swab: At the visit at 9 months of age, we will use a cotton swab to go inside your child's nose. We will check to see whether your child is carrying any bacteria that cause acute upper respiratory disease. All children are vaccinated against this disease, so even if your child has this bacteria, it does not mean that he or she is sick. We are testing to see whether your child has an adequate response to the vaccine.

Sick visits: We ask you to bring your child to this clinic if your child is ill at any time during the study. In the event of an emergency, you should bring your child to the nearest health facility or hospital. We also have staff in the following health clinics: Abidha, Ongi'elo, Lwak, and Saradidi. In case of illness after the clinic closes, at night, or on the weekend, we will have a nurse on-call at St. Elizabeth's Lwak Hospital to see your child. If your child requires hospitalization, we will provide transport for the child to be taken to New Nyanza General Provincial Hospital. We will pay for the child's hospitalization at these hospitals for malaria, lack of blood, worms, diarrhea, and pneumonia illnesses.

We would prefer you not to buy any routine treatment for malaria or treatment for lack of blood from shops or clinics during the study unless necessary. We ask this because extra medicine may result in side effects for your child. Other drugs may also reduce the effect of the study drugs. We supply all other drugs for malaria, lack of blood, worms, diarrhea, and pneumonia free of charge at the health clinic. Therefore, it will usually not be necessary to buy other medicines for those conditions.

Risks: All medicine has side effects.

General: There is some chance of vomiting after any of the study drugs. If this occurs within 30 minutes, then your child will be given another dose of the drug. If the vomiting occurs later than 30 minutes, no additional drug will be given.

Iron: Some children do not like the taste of iron. Some children complain of nausea and not feeling like eating after taking iron. In some children the teeth will become darker. In other children the stool will become darker or greener than normal. This is a normal reaction to treatment with iron. The teeth and stool color will become normal again after the iron treatment is completed. Iron is also toxic if taken in large doses (more than recommended amount).

Fansidar: Sometimes a child may get a rash after treatment with Fansidar®, one of the study medicines. If this occurs, we will stop the medicine and recommend that your child be treated with different malaria medicines in the future.

Amodiaquine: There are no known specific risks of amodiaquine when taken intermittently to treat malaria.

Artesunate: There are no known specific risks of artesunate.

Lapdap: Sometimes a child can get a temporary anemia following Lapdap. We believe this risk to be small. However, as this is a newer drug, and has not been used often in children in Africa, the risks are not completely known.

Sugar pills: We expect no side effects with sugar pills.

Heel or finger prick: A small bruise or mild pain on the heel or finger from where the blood is taken may develop. There is also a chance of infection when blood is drawn. This chance is very small because we always use clean materials.

Nasal swab: There is a chance of local irritation, bleeding, or infection from the nasal swab.

Costs/compensation: If the event of any problem from the heel or finger prick or the nasal swab that a doctor needs to look at, or a severe reaction to the malaria drug treatment, we will provide transport to the hospital. In the hospital your child will be treated free of charge. No such incident has occurred since the beginning of the CDC studies in Asembo since June 1992.

Lab tests: All blood samples will be tested in Kisian for malaria. Part of the blood and the nasal swab may be stored and sent to labs in Europe and the USA. In the USA, further studies may be done that will help us to know more about how your body protects itself against malaria and lack of blood. This includes a study of how your child's body responds to vaccines. The nasal swab will be tested for bacteria. The blood may be tested for iron, response to iron, or response to malaria. Part of the blood will be sent to France to study your child's response to vaccines. If we get any results from these studies that may affect the health of

Initials.....

your child, we will inform you. Results of the G6PD test will not be given. All the lab tests will be done free of charge.

Privacy: If you want your child's blood sample taken out of storage, please let our study staff know. We will destroy the sample. This will have no effects for you or your child. The facts we collect in the study and the results of the lab tests will be kept private to the extent allowed by law. The child's name will not be used on any of the study reports or study samples. Only study personnel will have access to these records and samples.

Severe illness: This study involves children who are healthy. Children with severe illness today will not be included in this study but referred to one of the hospitals in the study area. Also if your child becomes very ill during the study because he has had a severe reaction to one of the study drugs we have given your child your child's participation in the study will need to be stopped.

Withdrawal from the study: Some children may be prescribed daily treatment with cotrimoxazole by a clinician. Cotrimoxazole may cause a serious reaction with one of our study drugs. Therefore, if your child begins taking daily cotrimoxazole, we will have to withdraw him or her from the study. This withdrawal will be done to safeguard the health of your child.

Stopping the study: You are free to choose for your child to be part of this study. If you do not want your child to be in the study, you have the right to refuse. If you do not want your child to go on with this study you can also stop anytime. This will have no effects for you or your child. You and your child can continue to receive regular care from this clinic.

Benefits: Your child will likely benefit from being in this study. Your child will receive free health care for malaria, lack of blood, worms, diarrhea, and pneumonia illnesses for a period of 24 months starting from the first day of this study. You will be given a "health passport" which allows your child to receive free treatment for these conditions in one of the study clinics for this period. The child will be seen by a special study nurse, which may result in shorter wait times for medical care. Inpatient hospital costs at Lwak and New Nyanza General Provincial hospitals will also be covered for enrolled children for medical conditions listed in sick visits section. Any other medical costs (such as specialty care or hospitalization for conditions not listed above or not resulting from one of the study medications) are not covered by the project. The free treatment and care at the hospital will help improve the health of your child. The free iron your child receives will probably help prevent lack of blood. Because your child will visit the clinic regularly during the course of the study, your child is also likely to have malaria detected and treated more quickly than usual. Your child will also be receiving malaria tests for febrile illnesses, which may allow for better treatment of these illnesses. You will be informed if your child has sickle cell

Initials.....

disease, which may help you seek needed care. We hope the results of this study will help to improve the treatment for malaria and lack of blood in this area.

Alternatives: You can choose not to have your child in this study. If you choose not to have your child in the study, your child will be seen by the regular staff in this clinic. He/she will get the standard MOH care and pay any standard fees. No further visits would be required.

Contacts: If your child has any problems from the study that you want a doctor to look at, you can contact Dr. Juliana Otieno at New Nyanza Provincial General Hospital. The telephone number is 23200. Should any further questions arise, or if you want to quit the study, please contact Dr. Larry Slutsker, Mr. Peter Otieno or Mr. Frank Odhiambo, at the CDC office in Kisian. The office is at Kisian, on the Kisumu-Busia Road. The telephone number is 22929, 22959, or 22983. If you have any questions about your rights as a study patient, or if you want to talk about the study with someone who is not part of this research project, please contact Dr. Margaret Oloo. Dr. Oloo is a special doctor for children and is not part of the study. You can also contact Dr. Margaret Oloo if you think your child has been injured because of this study. She works in the Aga Khan Hospital in Kisumu and can be reached by phone. The phone number is 057 41031.

Thank you very much for your time.

Initials.....

Malaria and Anemia Prevention Study:

The above has been explained to me and I have read the permission form or it has been read to me. I agree for my child to take part in the study. I have been told that I am free to choose for my child to be part of this study. I also have been told that if I do not want my child to go on with this study I can stop at anytime. This will have no effect on future care that I might receive for my child or me. I agree for my child's blood to be tested for malaria, lack of blood and factors that may protect against malaria, lack of blood, or bacterial infections. I agree for my child's nasal swab to be tested for bacteria.

Parent/Guardian	Name..... Initials.....	Signature..... Mark*	Date.....
IPTi Registrar	Name.....	Signature.....	Date.....
Independent witness*	Name.....	Signature..... Mark**	Date.....

**A parent can sign or make a mark and have his/her permission confirmed by the signature of a witness.
** A mark is made by the parent or guardian by thumbprint (placing their thumb on an inepad and pressing down in the space above)*

Either mother or father or guardian can sign. All not required. Witness only required for those who cannot sign. All pages of the consent form must be initialed by the mother, father, or guardian (the person who signs the consent form).

Initials.....

Long-term storage and future studies:

We would like to store your child’s leftover blood to do more tests related to malaria in the future. No HIV or genetic testing is planned. It is your choice to let us keep the blood after the study ends. You can still be part of the study if you do not want us to store the blood. At the end of this study, we will take your name off of all forms. Therefore, we cannot report any new test results on the stored blood to you.

If you change your mind about saving blood while the study is ongoing, we can destroy the blood. To do this, contact Mr. Peter Otieno, Mr Frank Odhiambo, or Dr. Mary Hamel at the CDC office in Kisian. The office is at Kisian, on the Kisumu-Busia Road. The telephone number is 22929, 22959, or 22983

Parent/Guardian	Name..... Initials.....	Signature..... Mark*	Date.....
IPTi Registrar	Name.....	Signature.....	Date.....
Independent witness*	Name.....	Signature..... Mark**	Date.....

**A parent can sign or make a mark and have his/her permission confirmed by the signature of a witness.*

*** A mark is made by the parent or guardian by thumbprint (placing their thumb on an inepad and pressing down in the space above)*

IPTi - Malaria Prevention Study

01 - Screening Form

Scanned &
Verified

Registrar code

Screening date (dd/mm/yyyy)

 / /

Health facility

- ☐ Lwak ☐ Abidha
☐ Ong'ielo ☐ Saradidi

date_01

regcode

hfac_01

gender

pentopv1

age5_14

parent

catch_area

sleep

willing_01

Part 1: Screening

1.00 Infant's gender ☐ Male ☐ Female

1.01 Is the infant here to get Pentavalent 1 or OPV 1?

Check their immunization card.

1.02 Is the infant between 5 and 16 weeks of age?

1.03 Is the infant with his/her parent or guardian?

Ask the guardian the name of the village they stay in:

1.04 Is the village listed in the catchment area?

Look up the name on the list of clinic catchment areas.

1.05 Are the guardian and the infant regular residents of that village?

1.06 Is the parent or guardian willing to join the study?

☐ yes☐ no**If 'yes',****continue****If 'no', STOP. DO NOT ENROLL****go to 3.04a.**

1.07 Does the infant have a sulfa allergy or any known allergies to any of the following drugs: Fansidar, Cotrimoxazole, sulphadoxine/pyrimethamine, quinine, or amodiaquine)?

1.08 Is the infant taking cotrimoxazole (prophylactically indefinitely) on a daily basis?

1.09 Will the infant be away from the study area (Asembo) for more than 6 months during the next two years?

☐ yes☐ no☐ yes☐ no☐ yes☐ no☐ yes☐ no☐ yes☐ no

If all the answers of questions 1.01-1.05 are 'yes', go to 1.06. CONTINUE

If any answers of questions 1.01-1.05 are 'no', STOP. DO NOT ENROLL

☐ yes☐ no☐ yes☐ no☐ yes☐ no

If any answers to question 1.07-1.09 are 'yes', STOP. DO NOT ENROLL

If all the answers of questions 1.07-1.09 are 'no', take to the nurse. CONTINUE

allergy

cotrimox

away

Part 2: Examination

Nurse code

nursecode

2.01 Has the infant had convulsions (*talarieya*) within the last day?

2.02 Does the infant have diarrhoea?

2.03 Does the infant have any difficulty feeding?

2.04 Does the infant appear seriously ill?

☐ yes☐ no☐ yes☐ no☐ yes☐ no☐ yes☐ no

If any of the answers of questions 2.01-2.04 are 'yes', use IMCI algorithm to assess.

If all the answers of questions 2.01-2.04 are 'no', CONTINUE

convulsion

diarrhoea

feeding

ill_serious

2.05 Is the infant being referred to the hospital today?

☐ yes☐ no

If 'yes', DO NOT ENROLL go to 3.01

If 'no', continue

hosp_ref

Screening / File Number

filenum_01

Registrar code

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regcode2

3.01 Is the child eligible (1.01-1.05 are 'yes' and 1.07-1.09 and 2.05 are 'no')?

☐ yes
If 'yes'
continue

☐ no
If 'no', STOP
DO NOT ENROLL

eligible

3.02 Is the parent or guardian willing to join the study?

☐ yes
If 'yes'
continue

☐ no
If 'no', STOP.
DO NOT ENROLL
go to 3.04a.

willing_02

Have the guardian read the consent form, or read the consent form to the guardian. Then, go through an Assessment of Participant Comprehension form.

3.03 Does the guardian comprehend the study?
(based on answers on the Assessment of Participant
Comprehension form).

☐ yes

☐ no
If 'no' STOP.
DO NOT ENROLL

comprehend

3.04 Does the guardian give consent to participate in the study?

☐ yes
If 'yes'
go to Part 4.

☐ no

consent

3.04a Why does the guardian not want to participate?

- ☐ needs to speak to husband
- ☐ worried about risk of HIV
- ☐ worried about risk of anaemia
- ☐ worried about effects of study drugs
- ☐ do not like or trust CDC
- ☐ other

--	--	--	--	--	--	--	--
- ☐ no reason

husband

HIV

anaemia

drugs

CDC

other

other_reason

no_reason

*** Note: Remember to refer the infant for immunization**

Part 4: Assignment of IPTi ID number

If the infant is eligible and the guardian has given consent, draw the next Study ID Card and record the number here. Then record the number on the Enrollment Form, blank Study ID Form and Clinic Intake Log.

IPTi Participant ID number

--	--	--	--

-

--	--

idnum

Take 2 photos of the infant and guardian and attach them on the Study ID Card and Form. Attach an IPTi Participant sticker to the Child Health Card(MOH Immunization Card).

Screening / File Number

--	--	--	--	--



IPTi - Malaria Prevention Study

02 - Enrollment Form

Scanned
& Verified

Registrar code

Interview date (dd/mm/yyyy)

 /

Health facility

☐ Lwak☐ Abidha☐ Ong'ielo☐ Saradidi

regcode

date_02

hfac_02

idnum

IPTi Participant ID number

 -

Record the number from the infant's study ID card.

Part 1: Family information

1.01 Infant's gender ☐ Male ☐ Female

1.02 Infant's date of birth (dd/mm/yyyy)

 /

sex

dob

1.03 Infant's name

Christian name

Juok name

Father's Juok name

1.04 Mother's name

Christian name

Juok name

Father / Husband's Juok name

name

namem

mname

mnamem

lname

lnamem

1.05 Head of compound name

Christian name

Juok name

Father's Juok name

1.06 Guardian's name (If not mother or head of compound)

Christian name

Juok name

Father / Husband's Juok name

cfname

gfname

cjname

gjname

clname

glname

1.07 What is the relationship of the guardian to the infant?

☐ mother☐ father☐ compound head☐ other relative☐ not related

guardian

If mother, continue. Otherwise go to 2.01.

1.07a During your last pregnancy, did you receive
2 doses of SP (Fansidar, Orophan,
Metakelfin, etc..) to prevent malaria during
pregnancy?

☐ yes☐ no☐ unknown

dose

Part 2: Location information

2.01 Which village do guardian and infant reside?

Name

Number

villname

village

2.02 Can the mother's permanent ID be found?

☐ yes☐ no**If yes, go to 2.03**

midfound

2.02a How long has the mother resided in Asembo?

☐ less than 1 month☐ 1-4 months☐ greater than 4 months☐ unknown

reside

2.03 Mother's Permanent ID

2.04 Compound

House (If unknown
leave blank)

mindividid

compound

house

2.05 Which landmarks does the child live near?

Complete Village Landmark Codemap.

File / Enrollment number

landmark1

landmark2

landmark3

landmark1

landmark2

landmark3

filenum_02

02 - Enrollment Form

Interview date (dd/mm/yyyy)

--	--	--	--	--	--	--	--	--	--

IPTi Participant ID number

--	--	--	--	--	--	--	--

date_02_2
idnum2

Part 3: Bednet Use

3.01 Do you have any bednets in your house?

☐ yes ☐ no ☐ unknown
**If no, complete Bednet Voucher
and go to part 4**

bednet

3.02 Did the child sleep under the bednet last night?

☐ yes ☐ no ☐ unknown
**If no, probe and complete Bednet
Voucher if necessary**

sleep

3.03 Was the bednet treated with insecticide within the last year?

☐ yes ☐ no ☐ unknown

treated

Part 4: Immunizations

Send the infant to receive his/her immunizations and ask them to return here after they are finished. Using the infant's MOH card, note the immunizations that were given today:

☐ OPV1 ☐ Pent1 ☐ none

opv1
pent1
notimmunized

Part 5: Samples

Nurse Code

Interviewer Code

--	--	--

--	--	--

nursecode

intcode

5.01 Is the child ill today?

☐ yes ☐ no

ill_today_02

5.02 Does the child appear ill today?
If 5.01 and 5.02 are both no, go to 5.09

☐ yes ☐ no

ill_now_02

5.03 Has the child had a hot body in the last 48 hours?

☐ yes ☐ no ☐ unknown

hotbody_02

5.04 Temperature

		.		°C
--	--	---	--	----

temp_02

5.05 Does the child have palmar pallor or other signs of anemia?

☐ yes ☐ no ☐ unknown

pallor_02

IF hot body in last 48 hours OR temp \geq 37.5 OR signs of anemia do Haemoglobin, OptiMal, and Blood Slide tests.

5.06 Hemoglobin

		.		g/dl
--	--	---	--	------

If < 11.0 give iron

5.07 OptiMal result

☐ positive ☐ negative
**If positive, note on Study ID
Card and give to Pharmacy
Technician**

5.08 Blood slide done

☐ yes ☐ no

hb_02

optimal_02

bloodslide

**ALL PARTICIPANTS
OBTAIN MICROTAINER SAMPLE
(red top)**

5.09 Blood sample number

--	--	--	--	--	--

Place label here:

--	--	--	--	--	--

5.09a Was blood sample taken before or after immunization?

☐ before ☐ after

bsampnum_02

taken

Part 6: Treatment

6.01 Was any antimalarial treatment (quinine) given?

☐ yes ☐ no

antimalaria_02

6.02 Was iron (ferrous sulfate) given?

☐ yes ☐ no

iron

Bring the infant back to the Registrar. Record the dates of the next IPTi visit on the IPTi Study ID card and Study ID Form. Give ID to guardian.

Date of next visit (dd/mm/yyyy)

--	--	--	--	--	--	--	--	--	--

nvisitdate_02

File / Enrollment number

--	--	--	--	--



03 - Scheduled Visit Form

Registrar code

Interview date (dd/mm/yyyy)

Health facility

☐ Lwak☐ Abidha☐ Ong'ielo☐ Saradidi

regcode

date_03

hfac_03

IPTi Participant ID number

Record the number from the infant's study ID card. If the guardian has not brought the ID card, please ask them to retrieve the card. If the ID card has been lost, look up the child in the files and create a new ID card.

idnum

Part 1. Study Visit - ALL VISITS**Which study visit is the infant here for today?**☐ Visit 2: Study drug 1 (OPV 2/Pent 2)☐ Visit 5: Study drug 3 (Measles)☐ Visit 7: Follow up (18 months)☐ Visit 3: Study drug 2 (OPV 3/Pent 3)☐ Visit 6: Follow up (12 months)☐ Visit 8: Follow up (24 months)☐ Visit 4: Follow up (18 weeks)

visitcode

☐ Visit 9: Missed medication ,Which study drug was this visit for?☐ Study drug 1☐ Study drug 2☐ Study drug 3

missdrug

Write the visit number on the top of all pages of this form.**Part 2. Location Information - ALL VISITS**

2.01 Child's name

Christian name

Juok name

Father's Juok name

Child's DSS Permanent ID

individid

2.02 What is the relationship of the caregiver to the infant?

☐ mother☐ baby sitter☐ other relative☐ unknown

caregiver

☐ father☐ maid (japidi)☐ other not related**If mother or father go to 2.04**

2.03 Are you (the caregiver) 15 years old or older?

☐ yes ☐ no ☐ unknown

cage15

If 'no', please tell them that they must get an older relative. STOP COMPLETION OF THE FORM. DIRECT TO IMMUNIZATION DESK IF APPROPRIATE.

Show the caregiver the village Landmark Code Map in the participant's file.

2.04 Has the infant moved to a new location since the last visit?

☐ yes ☐ no ☐ unknown

moved

If 'yes', record relocation information below and on a new Village Landmark Codemap. If 'no' go to Part 3.

2.04a In which village does infant and caregiver reside?

Name

Number

villname
village

2.04b Have you moved:

☐ new house and new compound in same village☐ new village within clinic catchment☐ new village in catchment of another clinic☐ outside study area**Contact Study Coordinator before continuing**

2.04c What is the name of the current head of compound?

wheremove

Christian name

cname

Juok name

cjname

Father's Juok name

cname

2.04d Compound House:

compound
house

2.04e Which landmarks does the infant live near?

landmark1

landmark2

landmark3

landmark1
landmark2
landmark3

File number

03-Visit Form

Visit Number

Interview date (dd/mm/yyyy)

IPTi Participant ID number

date_03_2
idnum2

Part 3: Immunizations - ALL VISITS

Using the infant's MOH card, note the immunizations that were given TODAY.
NOTE: If visit 5, blood sample must be taken before measles immunization is given.

☐ BCG ☐ OPV1 ☐ OPV2 ☐ OPV3 ☐ Pent1 ☐ Pent2 ☐ Pent3 ☐ Measles ☐ None

bcg opv1
opv2 opv3
pent1 pent2
pent3
measles
notimmunized
nursecode1

Part 4: Symptoms - ALL VISITS

Nurse code

- 4.01 Is the infant ill today?
- 4.02 Has the infant had convulsions within the last day?
- 4.03 Does the infant vomit everything?
- 4.04 Is the infant not able to drink or breastfeed?
- 4.05 Does the infant appear ill today?

<input type="radio"/> yes	<input type="radio"/> no
<input type="radio"/> yes	<input type="radio"/> no
<input type="radio"/> yes	<input type="radio"/> no
<input type="radio"/> yes	<input type="radio"/> no
<input type="radio"/> yes	<input type="radio"/> no
If any of the answers of 4.01-4.05 are 'yes', complete Sick Visit Form.	
If all the answers of questions 4.01-4.05 are 'no', go to 5.01.	

ill_today
convulsion
vomit
feeding
ill_now

Part 5: Treatment History - ALL VISITS

If Sick Visit form completed, do not fill part 5. Go to Part 6:

- 5.01 Was the child admitted to a hospital since the last time you visited an IPTi clinic? (since the last time you visited the IPTi study staff in this clinic, or another IPTi clinic). ☐ yes ☐ no ☐ unknown
If 'no', go to 5.02.
- 5.01a Was this admission facilitated by IPTi staff? ☐ yes ☐ no ☐ unknown
If no or unknown, fill Hospital Discharge Form.
- 5.01b Has your child had a blood transfusion since the last visit? ☐ yes ☐ no ☐ unknown
- 5.02 Has your child taken any medications in the past 2 weeks other than those given by study staff? ☐ yes ☐ no ☐ unknown
If 'no', go to Part 6.

admitted
facilitated
transfusion_03
medication

What was your child given?
Show caregiver Medication Reference Sheet and the probe for specific medications.

Where was it obtained?
1=this clinic, 2=other clinic, 3=hospital, 4=duka, 5=other

SP	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Amodiaquine	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Septtrin (CTX)	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Chloroquine	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Quinine	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Co-artem	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Cotexin/alaxin	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Cosumate	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Analgesics	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Antibiotic	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Antihelminthic	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Valium	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Other:	<input type="radio"/> yes	<input type="radio"/> no	<input type="radio"/> unknown	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4	<input type="radio"/> 5
Specify	<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>							
File number	<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>							

sp
sp_obt
aq
aq_obt
ctx
ctx_obt
cq
cq_obt
qu
qu_obt
co_artem
co_artem_obt
cotexin
cotexin_obt
cosumate
cosumate_obt
anal
anal_obt
antib
antib_obt
antih
antih_obt
valium
valium_obt
other
other_obt
other_name

Part 6: Intervention Drug - Iron - VISITS 2, 3, AND 4

Visit 2: Give 2 bottles of iron. Visit 3: Give 2 bottles of iron. Visit 4: Give 4 bottles of iron.

6.01 Was iron given?

☐ yes ☐ no

iron

Part 7: Intervention Drug - Antimalarial - VISITS 2, 3, 5 AND 9

7.01 Was study drug given as a Missed Medication dose (Visit 9) in the last 2 weeks?

☐ yes ☐ no

mm2wks

(check participant folder to note if any Visit 9)

If yes, do not give study drug.

7.02 Has the infant taken SP (Fansidar, Oraphan, Metakelfin, etc) in the last 2 weeks?
(refer to question 5.02)

☐ yes ☐ no ☐ unknown

sp2wks

If yes or unknown, do not give study drug.

7.03 Has the infant taken Amodiaquine(AQ) or chloroquine in the last 2 weeks?
(refer to question 5.02)

☐ yes ☐ no ☐ unknown

aq2wks

If yes or unknown, do not give study drug.

7.04 Has the infant taken Quinine, in the last 2 weeks?
(refer to question 5.02 and check if infant had an unscheduled sick visit in the last 2 weeks)

☐ yes ☐ no ☐ unknown

qu2wks

If yes or unknown, do not give study drug.

7.05 Has the infant taken Septrin(SEP), in the last 2 weeks? (refer to question 5.02)

☐ yes ☐ no ☐ unknown

ctx2wks

If yes or unknown, do not give study drug.

If no go to 7.06

7.05a Is the infant taking Septrin (prophylactically for an indefinite period) daily?

☐ yes ☐ no ☐ unknown

ctxdaily

If yes, WITHDRAW child from study.

If the infant was given a study drug or has taken SP, AQ, Quinine, chloroquine or SEP in the past 2 weeks (but is not taking SEP daily), calculate the date 2 weeks from the most recent date one of the drugs was administered and write it at the bottom of the next page as the next visit date. If the caretaker says she does not know when the drug was administered, calculate the date 2 weeks from today.

If the infant has not taken study drug, SP, AQ, Quinine, chloroquine or SEP in the last 2 weeks, give the study drug.

7.06 Was the study drug given?

☐ yes ☐ no

studydrug

Observe the infant for 30 minutes to determine if the dose was tolerated. If the dose was vomited, repeat the dose and observe the infant for another 30 minutes. Record all information about vomiting below:

7.07 Did the infant vomit the study drug?

☐ yes ☐ no ☐ left without being observed

vomit_sd1

If yes, give a second dose.

If no, go to part 8

7.07a Was a second dose of study drug given?

☐ yes ☐ no

studydrug2

If no, record why not given in Treatment Book

7.07a1 Was the second dose of study drug vomited?

☐ yes ☐ no ☐ left without being observed

vomit_sd2

If yes, do not give a third dose.

Part 8. Bednet use - ALL VISITS

Interviewer code

intcode2

8.01 Do you have any bednets in your house?

☐ yes ☐ no ☐ unknown

bednet_03

If 'no', go to Part 9.

8.02 Did your child sleep under a bednet last night?

☐ yes ☐ no ☐ unknown

sleep_03

8.03 Was the bednet "treated" with insecticide within the last year?

☐ yes ☐ no ☐ unknown

nettreat_03

File number

Part 9: Iron Taking Behavior - VISITS 3 AND 4

9.01 Does the infant have any difficulty taking the iron?	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> unknown	fe_dif1_03
9.02 Do you have any difficulty giving the iron?	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> unknown <input type="radio"/> NA	fe_dif2_03
9.03 How often has the infant been given the iron?	<input type="radio"/> never <input type="radio"/> rarely <input type="radio"/> occasionally <input type="radio"/> most days <input type="radio"/> daily <input type="radio"/> unknown	fe_often_03
9.04 Did you spill any of the iron since the infants last study visit?	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> unknown	fe_spill_03
9.05 Did you share the iron with other children or adults?	<input type="radio"/> yes <input type="radio"/> no <input type="radio"/> unknown	fe_share_03
9.06 Did you have the iron bottle with you?	<input type="radio"/> yes <input type="radio"/> no	fe_bottle_03
Write down the amount of iron remaining in the bottle	Bottle 1 <div></div> mm Bottle 2 <div></div> mm	fe_mm_03 fe_mm_03_2

Part 10: Clinical measurements - VISITS 2, 6, 7, AND 8

10.01 MUAC (If < 8 OR >20 Re-Measure)	<div></div> . <div></div> cm	muac
10.02 Length/ height (If < 40 OR >110 Re-Measure)	<div></div> <div></div> <div></div> . <div></div> cm	Length board number height boardnum
10.03 Weight (If < 2 OR >13 Re-Measure)	<div></div> <div></div> . <div></div> <div></div> kg	Weighing scale number weight scalenum

Part 11: Samples

IF VISIT 5	IF VISIT 6, 7 AND 8	IF VISIT 4, 5, AND 6
PERFORM NP SWAB	TEST HEMOGLOBIN	OBTAIN MICROTAINER SAMPLE (red top)
11.01 NP swab number <div></div> Place label here: <div></div>	11.02 Hemoglobin <div></div> . <div></div> g/dl If <8.0 and >=5.0 refer to Nurse for iron treatment. If <5.0, refer to Nurse for hospital referral	11.03 Blood sample number <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> Place label here: <div></div>
IF VISIT 2 AND 6 OBTAIN EDTA SAMPLE (Purple top)	11.02a Was iron given? <input type="radio"/> yes <input type="radio"/> no	IF VISIT 5 11.03a Was measles vaccination given before or after blood sample was taken? <input type="radio"/> before <input type="radio"/> after
11.04 Blood sample number <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> Place label here: <div></div>	IF VISIT 6, 7 AND 8 MAKE BLOOD SLIDE	IF VISIT 6, 7 AND 8 TAKE TEMPERATURE
IF VISIT 2 AND 6 OBTAIN FILTER PAPER SAMPLE	11.05 Blood slide done <input type="radio"/> yes <input type="radio"/> no	11.06 Temperature <div></div> <div></div> . <div></div> °C If > =37.5 °C complete Sick Visit Form if not already completed
11.07 Filter paper done? <input type="radio"/> yes <input type="radio"/> no	Calculate the date of the next study visit: File number <div></div> <div></div> <div></div> <div></div> <div></div> <div></div>	Date of next IPTi visit (dd/mm/yyyy) <div></div> <div></div> / <div></div> <div></div> / <div></div> <div></div> <div></div> <div></div> <div></div> nvisitdate_03

IPTi - Malaria Prevention Study
05 - Compliance Monitor - Intervention Form

IPTi Participant ID number

				-		
--	--	--	--	---	--	--

Date (dd/mm/yyyy)

		/			/				
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Health facility

☐ Lwak ☐ Abidha idnum

☐ Ong'ielo ☐ Saradidi date_05

hfac_05

nursecode

Nurse code

--	--	--

Part 1. Location Information

Record the details below from the Study ID Form.

1.01 Child's name

Christian name

Juok name

Father's Juok name

Infants' Date of birth(dd/mm/yyyy)

_____/_____/_____

1.02 Head of Compound

Christian name

Juok name

Fther's Juok name

1.03 Village Compound House

1.04 Which landmarks does the infant live near?

Landmark 1 Landmark 2 Landmark 2

IPTi - Malaria Prevention Study
05 - Compliance Monitor - Intervention Form

IPTi Participant ID number

-

Date (dd/mm/yyyy)

/

/

idnum2

Which study visit is this intervention for?

☐ Visit 2: Study drug 1 (OPV 2/Pent 2) ☐ Visit 3: Study drug 2 (OPV 3/Pent 3)

visticode

☐ Visit 5: Study drug 3 (Measles)

☐ Visit 9: Missed medication

filenum03

Was iron given?

☐ yes ☐ no

If visit 9, copy filing number
from Scheduled Visit Form

irong

Day 2

Attempt	Date (dd/mm/yyyy)	Compliance Monitor	Is child found?	If no, why not?
1	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>	<div><div></div><div></div><div></div></div>	<input type="radio"/> yes <input type="radio"/> no	
2	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>	<div><div></div><div></div><div></div></div>	<input type="radio"/> yes <input type="radio"/> no	

attemp1day2

cmcode2_1

found2_1

attemp2day2

cmcode2_2

found2_2

If child not found after 2nd attempt, begin attempting to give Day 3 treatment

IPTi ID number	Study drug given?	1st Dose Vomit?	2nd Dose Given?	2nd Dose Vomit?	Intervention Observed ID code	Date (dd/mm/yy)
<div><div><div></div><div></div><div></div><div></div></div><div>-</div><div><div></div><div></div></div></div>	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<div><div><div></div><div></div></div></div>	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>

idnum2_1

given2_1

vomit2_1

given2_2

vomit2_2

treatcode2

dosedate2

If 1st dose is vomitted return to clinic to get the 2nd dose (if weekend or holiday bring the child to Lwak)

Day 3

Attempt	Date (dd/mm/yyyy)	Compliance Monitor	Is child Found?	If no, why not?
1	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>	<div><div></div><div></div><div></div></div>	<input type="radio"/> yes <input type="radio"/> no	
2	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>	<div><div></div><div></div><div></div></div>	<input type="radio"/> yes <input type="radio"/> no	

attemp1day3

cmcode3_1

found1

attemp2day3

cmcode3_2

found3_2

If child not found after 2nd attempt, notify Field Supervisor

IPTi ID number	Study drug given?	1st Dose Vomit?	2nd Dose Given?	2nd Dose Vomit?	Intervention Observed ID code	Date (dd/mm/yy)
<div><div><div></div><div></div><div></div><div></div></div><div>-</div><div><div></div><div></div></div></div>	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<input type="radio"/> yes <input type="radio"/> no	<div><div><div></div><div></div></div></div>	<div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div><div>/</div><div><div></div><div></div></div></div>

idnum3_1

given3_1

vomit3_1

given3_2

vomit3_2

treatcode3

dosedate3

If 1st dose is vomitted return to clinic to get the 2nd dose (if weekend or holiday bring the child to Lwak)

IPTi - Malaria Prevention Study
11- Parasite Density Form - A
1st & 2nd Reading

Scanned
& Verified

IPTi ID Number Date (dd/mm/yy) (Date on slide)	Reading 1				Reading 2				C o m m e n t																																																																																																																																								
	Asexual Parasites		Gametocyte Parasites		Asexual Parasites		Gametocyte Parasites																																																																																																																																										
	Pos/Neg Lab code	Species Density/500WBC	Pos/Neg	Species Density/500WBC	Pos/Neg Lab code	Species Density/500WBC	Pos/Neg	Species Density/500WBC																																																																																																																																									
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IPTi - Malaria Prevention Study
11- Parasite Density Form - A
1st & 2nd Reading

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IPTi ID Number Date (dd/mm/yy) (Date on slide)	Reading 3						Comments
	Asexual Parasites			Gametocyte Parasites			
	Pos/Neg Lab code	Species Density/500WBC		Pos/Neg	Species Density/500WBC		
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NOTE: If neg is marked for asexual or gametocyte parasites, then density/500 wbc does not have to be filled

IPTi - Malaria Prevention Study
11- Parasite Density Form - B
3rd Reading

IPTi ID Number Date (dd/mm/yy) <i>(Date on slide)</i>	Reading 3				Comments
	Asexual Parasites		Gametocyte Parasites		
	Pos/Neg Lab code	Species Density/500WBC	Pos/Neg	Species Density/500WBC	
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idnum
date_11

aspres3
labcode3

aspeci3
asdens3

gmpres 3

gspeci3
gmdens3

NOTE: If neg is marked for asexual or gametocyte parasites,
then density/500 wbc does not have to be filled

IPTi - Malaria Prevention Study
12- Withdrawal/Suspension Form

IPTi Participant ID number

 -

Date (dd/mm/yyyy)

 / /

Health facility

☐ Lwak

☐ Abidha

☐ Ong'ielo

☐ Saradidi

Clinic Staff Code

idnum
date_12
hfac_12

intcode

Part 1: Child is to be withdrawn/suspended

1.01 Is this child:

☐ No longer an active participant (suspended)?
Complete question 1.02

active

☐ Withdrawing from the study?
Complete question 1.03

☐ Deceased?

Date deceased(dd/mm/yyyy)

 / /

dod

1.02 Active looking (suspension) for the child has stopped

stopped

- ☐ The child has missed 1 scheduled visit and the Compliance Monitor was unable to locate the child and suspects the child has moved out of the catchment area
- ☐ Caregiver has informed us that the child has moved outside the study area

1.03 This child is being withdrawn from the study because:

withdrawn

- ☐ Adverse reaction to study drugs
- ☐ Guardian refuses further participation without further explanation
- ☐ Infant is taking daily cotrimoxazole prophylaxis indefinitely
- ☐ Guardian refuses further participation with explanation:

explanation

☐ Other:

Part 2: Suspension is to be lifted

2.01 File number of the suspension form

filenum_12_2

2.02 Reason suspension is lifted

- ☐ Child has moved back into the study area
- ☐ Child has started coming to clinic again

reason_lift

File/withdrawal number

filenum_12

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15 - Parental Consent Form

IPTi Participant ID number

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Oboke Mar Yudo Thuolo Koa Kuom Janyuol Kata Jarit Nyathi Ma Oyie Ni Nyathine Odonji E Nonro Mar Geng'o Malaria Kod 'Nok Mar Remo' Ne Nyithindo (IPTi)

Wach motelo

Kenya Medical Research Institute (KEMRI) to kod Centers for Disease Control and Prevention, USA (CDC) timo nonro mar ng'eyo yo maber mogik mar geng'o 'nok mar remo' (anemia) kod malaria. E nonroni wadwaro pimo yore mopogore opogore minyalo geng' go tuo mar malaria kod 'nok mar remo'. Achiel kuom yedhe ma wamiyo nyithindo en yadh remo ma iluongo ni iron. Yedhe mamoko gin Fansidar® kod artesunate, amodiaquine kod artesunate, kod Lapdap®. Adek gi duto gin yedhe ma osepudhi, kendo ma itiyogo e thiedho malaria. Fansidar, amodiaquine, kata yadh remo (iron) gin yedhe mayudore mayot kendo inyalo ng'iewgi e duke mang'eny ei Asembo ka. Artesunate kod Lapdap to ok us e duke mang'eny. Wadwaro ng'eyo ni ka Fansidar + artesunate, amodiaquine + artesunate, kata Lapdap, kochiw kod yadh remo to nyalo bedo maber molooyo kochiw yadh remo kende kuom geng'o 'nok mar remo' kuom nyithindo mayom. Bende dwaher ng'eyo kapo ni yedhe gi kelo lokruok e yo ma dend nyathi winjore gi chenjo. Nonroni biro kawo nyithindo mayom madirom elufu achiel gi mia abich (1500).

Grube mag thieth

Nyithindo duto ma okaw e nonroni ibiro pogi e grube ang'wen ka okwanygi radha radha ma jo nonro kata janyuol nyathi ok bi yiero bende ok bi ng'eyo ni nyathi bedo e grup mane nikech ma nyalo chando duoko mawuok e nonro. Grup ka grup biro yudo yadh malaria ma opogore. Grup moro biro yudo Fansidar gi artesunate, moro biro yudo amodiaquine kod artesunate, machielo biro yudo Lapdap, moro bende biro yudo placebo (gima olosi ma oriw gi sukari to yath onge e iye). Kata kamano nyithindogi duto te ibiro thiedhi kod yadh remo (iron) kuom dweche ang'wen.

Nyithindo ei grube ang'wen gi te ibiro mi yedhe ma oregi e yor amadha ka gin gi jumbe 10, jumbe 14 kod dweche 9. Yedhe moko ibiro mi nyathi e od thieth, to moko obiro muonyo chieng' maluwo mano kendo moko omuonyo chieng' mar adek. Jatich nonro biro limi dala mondo okelne nyathini yedhegi chieng' mar ariyo gi chieng' mar adek. Jotich nonro kata in janyuol/jarit nyathi ok bi ng'eyo yedhe ma nyathini yudo nyaka chop nonro rum.

Kaka ibiro kelo nyathi

E nonroni wabiro kwayi mondo ikel nyathini e od thieth ka nya dibiriyo (ka nyathini ni gi jumbe 10, 14 kod 18 kendo kochopo dweche 9, 12, 18 gi 24). E limbe ka limbe jatich nonro biro penji penjo kaluwore gi ngima mar nyathini kendo obiro nono nyathi. E limbe moko jatich mar nonro biro pimo pek kod bor mar nyathi. E limbe moko jatichni biro chuoyo lith lwedo kata ombong' tiend nyathini mondo okaw remo matin. Kendo e limbe moko ibiro mi nyathini yadh nonro. Limbe ka limbe biro kawo thuolo madirom dakika 30.

Nukta mochung ne nying Janyuol/Jarit

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Yedhe nonro

E limbe mar chenjo mar nyathi e juma mar10,14 kod mar dweche 9, nyathini biro yudo thieth e od thieth. Bang'e, jatich nonro biro limi dala kuom ndalo ariyo moluwore mondo ochiw ne nyathi yath modong'. Seche duto ma omi nyathini yadh nonro, jatich nonro biro ng'iye kuom dakika 30 mondo ong'e adieri ni nyathi ok ong'ok kata obedo matuo. Ibiro yudo chupa mar yadh remo (iron) e juma mar10, mar 14 kendo mar 18. Dwaher ni imi nyathini yadhni pile pile. Ka nyathini ni gi dweche 6, wabiro limo odi mondo wanon ka nyathini osemi yedhe remo gi duto te.

Remo ma wakawo

Kawuono wabiro chuoyo ombong' tiend nyathini kata lith lwete mondo wakaw remo ma wapimo. Wabiro timo kamano kendo ka en ja jumbe 10,18 kod ka en ja dweche 9 kod 12. Remo mawabiro kawo tin, madirom 1/4 mar kijiko chai kende. Remoni wabiro kano. Moko wabiro tiyogo mondo wang'i kaka dend nyathini rwako chenjo. Moko kuom remo ni wabiro tiyogo mondo opimgo tuo mar remo milwongo ni amara (sickle cell). Ibiro nyisi ka po ni nyathini ni gi amara.Wabiro chiwo johochi mondo okonyi ng'eyo kaka inyalo manyo ni nyathini yore thieth kendo kaka inyalo rito nyathini e dala. Remo moko ibiro tigo kuom pimo gigo mamoko e del manyalo kelo 'nok mar remo' ne nyithindo, kaka tin mar G6PD.

E limbe mar juma mar 10 to kod mar dwe mar 12, wabiro tono remb nyathini matin e kalatas moro matin. Wabiro pimo remo ma oton e kalatasno mondo okonywa ng'eyo mang'eny kaka yedhe ma itiyogo kuom thiedho malaria tiyo e gweng'u ka.

Ka nyathi ochopo dweche 12, 18 kendo gi 24 wabiro kawo oton mar remo madirom ondeng' 5 mondo wapim kadipo ni nyathini nigi malaria kod / kata 'tin mar remo'. Wabiro chiwo thieth ka nyathini ni gi tin mar remo, malaria, kata del ma ore. Ma wabiro timo e seche ma ibiro e limbe gi.

Ramien Um

E limbe mar dweche 9 bang' nywol nyathi, wabiro soyo pamba e ume.Wabiro ng'iyo ka nyathini ni gi kute manyalo kelo tuoche mamako kor, kata machando yueyo mar nyathi. Nyithindo duto yudo chenjo mar tuoni, omiyo kata ka nyathini oyudi gi kute gi, ok onyiso ni obiro yudo tuoni. Bende wabiro pimo nyathi mondo wane kaka dende rwako chenjo.

Limbe ka nyathi tuo

Wakwayi ni ikel nyathini e od thieth saa a saya ma nyathini tuo kapod nonroni dhi nyime. Kadipo ni nyathini obedo matuo kendo odwaro thieth mapiyo to itere kar thieth kata osiptal machiegni kodi mogik. Nonroni ni kod jotich e kuonde thieth mag Abidha, Ong'ielo, Lwak kod Saradidi. Ka tuo dipore ne nyathi gotieno ka ose lor od thieth, kata chieng' jumamos gi jumapil, wabiro bedo gi jathieth e osiptal mar St Elizabeth Lwak, ma nyalo thiedho nyathino. Ka nyathini dwaro thieth momedore ma dwaro ni orwake e osiptal mondo othiedhe to wabiro chung'ne eyo manyalo tere New Nyanza General Provincial Hospital. Wabiro kawo chudo mar ospital ka nyathini orwak kuro

Nukta mochung ne nying Janyuol/Jarit

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Kapod nonroni dhi nyime, wabiro kwayi ni kik inyiew ne nyathini yedhe mag thieth mar malaria kata nok mar remo e duke kata od thieth , mak mana kochuno ahinya. Wakwayo kama nikech medo yedhe moko e wi magwa nyalo kelo chandruok ni nyathini. Yedhe mamoko bende nyalo duoko teko mar yedhe nonroni piny. Wachiwo yedhe dutomoko go te mag malaria, 'nok mar remo', njofni, to kod Numonia (kor mathung') maonge chudo moro amora e od thieth. Kuom mano, biro bedo maonge tiende nyiewo yedhe mamoko mag tuoche gi.

Chandruok manyalo bedo: Yedhe duto ni kod richo gi

Kuom yedhe duto: Nyalo pore ni ng'ato ng'ok bang' kawo yedhe moro amora mar nonro. Ka ma otimore kochopo kata kapodi kochopo dakika 30 to ibiro mi nyathini yadhno kendo. Ka ong'ok bang' dakika 30 to ok bi mede yath moro.

Yadh remo(Iron): Nyithindo moko ok ohero bilo yadh remo. Nyithindo moko wacho ni giwinjo ka chuny gi lew to kendo giwinjo kama ok gidwar chiemo bang' madho yadh remo. E nyithindo moko, lake gi lokore marateng'. To moko oko maduong' mar gi lokore marateng' kata majan moloyo pile. Ma en gima timore pile ma ok lich ka ng'ato ithiedho gi yadh remo. Rangi mar lak kata oko maduong' biro duogo e wang'e ka thieth gi yadh remo ose tieki. Yadh remo be en sum kendo onyalo hinyo ng'ato kokaw mang'eny mokalo karom madwarore.

Fansidar: Seche moko dend nyathi nyalo rwodho bang' thieth gi Fansidar®, ma en achiel kuom yedhe mar nonroni. Ka ma otimore, wabiro chungo miyo nyathi yadhno kendo wabiro golo paro ni nyathini othiedh gi yedhe malaria mopogore ndalo mabiro.

Amodiaquine: Onge chandruok ma ong'ere maluwore gi muonyo amodiaquine e seche mopogore opogore kuom thiedho malaria.

Artesunate: Onge chandruok mong'ere maluwore gi muonyo artesunate.

Lapdap: Seche moko nyathi nyalo bedo gi nok mar remo kuom saa matin bang' kawo Lapdap. Wan gi paro ni chandruok machalo kama nyalo bedo matin nono. Mak mana ni yadhni en yath manyien, kendo pod ok oti kode mang'eny kuom nyithindo e Afrika ka, omiyo ok wanyal ng'eyo chandruok te manyalo bedo kuom tiyo kode.

Gima olosi gi sukari maneno kaka yath to yath onge e iye: Ok wapar ni chandruok moro amora biro wuok e tiyo gi gini.

Chuoyo ombong' tielo kata lith lwedo: Kama ochuo e ombong' tielo kata lith lwedo kuom kawo remo nyalo dong' gi alama matin kendo be inyalo winjo rem matin. Nyalo timore ni tuoche moko nyalo donjo e del kogol remo kama. Mak mana ni timruok kuom gima kama tin ahinya to nikech watiyo gi gik maler pile.

Ramien um: Nyalo timore ni rewni moro matin nyalo wuok kama ramien um biro kale. To bende chwer kata tuo nyalo donjo kaluwore gi tiyo gi ramien um.

Thieth ma onge Chudo:

Kaponi nitiere chandruok mowuok kuom chuowo ombong' tielo/lith lwedo kata yueyo um gi pamba ma dwarore ni daktari ong'i, kata ka rach moro owuok kuom muonyo yedhe malaria mawathietho go, wabiro chung'ni e yor wuoth kendo wabiro tero jatuo e ospital. E osiptal nyathini ibiro thiedho nono maonge chudo moro amora. Onge chandruok machalo kamano mose wuok kata timore chakre jo CDC chak nonrogi ei Asembo e dwe mar auchiel e higa 1992. E limbe mag klinik duto ma ochiki, ibiro miyi pesa mar wuoth ma oromi biro e Klinik kendo dok dala ka itiyogi gi ngware kata boda boda. Kamano bende ibiro miyi pesano e saa asaya ma ikelo nyathi e klinik nikech ong'ogo yath nonro.

Pimo Tuoche (Lab tests)

Remo duto mokaw ibiro ter e od pimo tuoche ma Kisian mondo opim ka gin kod malaria. Remo moko gi pamba mar ramien um inyalo kan mondo obi oori e kar pimo tuoche (lab) manitiere Europe kod USA. E piny mar USA, nonro matut inyalo tim mabiro konyowa ng'eyo mang'eny molooyo kuom kaka dend nyathini geng'o tuoche mag malaria kod nok mar remo. Ma oriwo nonro kuom kaka dend nyathini winjore gi chenjo. Ramien um bende ibiro pim mondo one kanikod kute makelo tuo. Remo bende inyalo pimgo kar rom yadh remo manie del (iron), lokruok manitiere bang' tiyo gi yadh remo(iron) kata kaka dend nyathi kedo ka malaria odonjo. Remo moko ibiro ter e piny mar France mondo onon kaka nyathini winjore gi chenjo. Kawayudo duoko moro amora kuom pimgi manyalo bedo gi wach kuom ngima nyathini to wabiro wachoni. Duoko mar pim mar G6PD to ok bi chiw. Pim tuoche duto ibiro tim nono maonge chudo moro amora.

Kano wach ma opondo

Kaponi idwaro ni remb nyathini ogol e kar keno to yie mondo inyis jotich nonro. Wabiro ketho remo go kendo ok bi kan gi. Ma ok bi kelo rach moro ne nyathini kata ne in. Weche ma wachoko e nonroni to gi duoko ma wayudo e pim mar tuoche ibiro kan maber kendo ok bi landi kaluwore gi chik Sirikal. Nying nyathi bende ok bi tigo e nonro kata duoko mabiro wuok kuom nonro. Jo matiyo e nonro kende e mabiro bedo gi thuolo mar neno gik mawayudo ka nonro dhi nyime.

Nyithindo ma tuo ahinya:

E nonroni ibiro kaw nyithindo ma ngima gi ber. Nyithindo ma tuo ahinya kawuono ok bi kaw e nonroni to ibiro nyis gi mondo gimany thieth e osiptal manitiere machiegni. E seche ma nonroni dhi nyime, ka nyathi ma osekaw e nonro obedo matuo ahinya nikech dende ok owinjore gi yedhe nonro ma wamiye to wabiro chunghe mondo kik odhi nyime gi nonro.

Wuok e nonro

Nyithindo moko nyalo bedo ma laktar ondiko mondo omigi yath ma iluongo ni cotrimoxasole pile pile. Yath mar cotrimoxasole ok winjre maber gi achiel kuom yedhe

Nukta mochung ne nying Janyuol/Jarit _____

ma wabiro chiwo e nonroni. Omiyo ka nyathini oketi e yath mar cotrimoxasole mondo omuony pile pile to wabiro gole oko e nonro. Ma wabiro timo mondo wakony ngima nyathini.

Chungo nonro: In kod thuolo mar yie kata dagi mondo nyathini obed e nonroni. Ka okidwar ni nyathini obed e nonroni to in kod adieri mar tamori. Bende ka okidwar ni nyathini odhi nyime gi bedo e nonroni to inyalo chungu saa asaya. Ma ok bi kelo rach moro amora ne in kata ne nyathini. In kata nyathini podi ubiro yudo thieth makare e od thieth ni.

Ber mawuok e nonroni: Nitiere ber ma nyathini nyalo yudo kuom bedo e nonroni. Obiro yudo thieth manono mar malaria, nok mar remo, njofni, diep gi tuoche mag kor mathung' kuom dweche 24 kochakore chieng' mokuongo mar nonroni. Ibiro miyi otiko mar yudo thieth mabiro miyo nyathini yudo thieth ma nono ka en gi tuo moro amora kuom ma wasewachogo e kuonde thieth ma nonroni timoree. Nyathini ibiro thiedhi gi jathieth mar nonroni kendo ma biro miyo ka rito thieth kawo seche matin molooyo pile.

Ka nyathi ma enonroni oruaki e wuod e osiptal ma Lwak kata New Nyanza General Provincial hospital ka en gi achiel kuom tuoche ma ondiki ebwo "limbe ka nyathi tuo", nonroni biro chulo chudo madwarore kuom nyathino. Kata kamano chudo mag thieth kuom tuoche moko ma opogore gi ma wasewacho go (kata ma ok obiro nikech tiyo gi yedhe nonro) to nonroni ok bi chulo. Thieth manono gi rit biro konyo ngima nyathini bedo maber. Yadh remo(iron) manono biro geng'one nyathini bedo gi tuo mar nok remo. Nikech nyathini biro limo od thieth kuom ndalo mang'eny ka nonroni dhi nyime, biro bedo mayot molooyo mondo oyud ka en kod malaria kendo ibiro tim ne thieth mapiyo molooyo pile.

Nyathini bende ibiro timne pim mar malaria ka en kod tuoche maluwore kod del maoore to mani nyalo miyo oyudi thieth maber molooyo kuom tuoche gi. Ibiro nyisi bende ka nyathini ni kod tuo mar amara (sickle cell) to ma nyalo konyi mondi imany yore mag rit kuom tuo ni ma dwarore. Wageno ni duoko mar nonroni biro konyo mondo thieth mar malaria kod nok mar remo obed maber molooyo e gweng'ni.

Paro Machielo: In thuolo yiero mondo kik nyathini obedi e nonroni. Ka iyiero mondo kik nyathini obedi e nonroni to ibiro nene gi jotich matiyo ka pile kendo obiro yudo thieth mowinjore kaka migawo mar rito ngima oyango, ka ichulo pesa ma owinjore. Limbe mag nonroni koro ok bi chan nii.

Joma inyalo tudori go: Ka nyathini ni gi chandruok moa kuom nonroni madiher ni laktar ong'i wachne to inyalo tudori gi Dr. Juliana Otieno ma tiyo New Nyanza Provincial General Hospital e namba simo mar 057 2023200. Kapod in kod penjo moko, kata ka idwaro mondo iwuogi e nonroni, to tudri kod Dr. Larry Slutsker, Mr. Peter Otieno kata Mr. Frank Othiambo e ofis CDC manitiere Kisian. Ofis ni nitiere Kisian e ndara maduon' ma wuok Kisumu ka dhi Busia. Namba simo gin 057 2022929, 057 2022959, kata 057 2022983. Ka in kod penjo ma oluwore gi adieri mari kaka achiel kuom jogo ma itimo ne

gi nonro, kata ka idwaro loso kuom nonroni kod ng'ano ma ok omakore gi nonroni to tudri gi Dr. Margaret Oloo. Dr. Oloo en jathieth manimba mochung'ne nyithindo to ok en achiel kuom jogo matimo nonroni. Bende inyalo tudori kod Dr. Margaret Oloo ka iparo ni nyathini ohinyore nikech nonroni. En otiyo Aga Khan Hospital ei Kisumu kendo inyalo yude e namba simo ma 057 20 41031.

Ero kamano kuom kawo sehegi.

Nonro mar gengo Malaria kod Nok mar Remo		
Mondik malo gi te oselerna kendo asesomo oboke mar ayie kata osesome ni an. Ayie ni nyathina obed e nonroni. Owachna ni an kod thuolo mar yiero mondo nyathina obedie nonroni. Owachna ni bende ka ok adwar mondo nyathina odhi nyime gi bedo e nonro to anyalo chung e saa asaya. Ma kotimore to onge wach moro amora mabiro tamo nyathina kata gi an kuom yudo rit makare ndalo mabiro. Ayie ni opim remb nyathina kanikod malaria, 'nok mar remo' kod gigo manyalo geng'e kuom yudo malaria, 'nok mar remo' kata tuoche mokel gi kute. Ayie ni ramien moa e um nyathina opim kanikod kute makelo tuo.		

Janyuol/Jarit	Nyinge Nukta ma ochung ne nyinge	Sei Alama*	Tarik / /
Ja ndiko mar IPTi	Nyinge	Sei	Tarik / /
Ja neno*	Nyinge	Sei Alama**	Tarik / /
<p>*Janyuol nyalo keto seyi kata keto alama kod janeno bende biro keto seyi mare manyiso ni janyuol/jarit nyathi oyie.</p> <p>** Alama miketo gi janyuol kata jarit nyathi en mar lwedo (placing their thumb on an inkpad and pressing down in the space above)</p>			

Kano remo mar tiyogo e nonro e kinde mabiro

Dwaher mondo wakan remb nyathini moko modong' mondo watingo nonro e kinde mabiro e weche momakore gi tuo mar malaria. Ok wapim kute mag Ayaki kata chwech remo. In thuolo yiero mondo iyienwa wakan remb nyathini. To pod inyalo mana bedo e nonroni kata ka ok iyie mondo wakan remb nyathini mar tiyogo e nonro e ndalo mabiro. E rumb nonroni, wabiro golo nyingi e oboke duto mag nonroni, omiyo ok wabi duokoni duoko moro amora mowuok kuom pim mar remo ma okan.

Ka iloko pachi ni ok idwar mondo wakan remb nyathini e kinde ma nonroni dhi nyime to itudri gi Mr Peter Otieno, Mr Frank Odhiambo, kata Dr Mary Hamel e ofis CDC ma Kisian mondo kik wakan remono. Ofis CDC ma Kisian ni e bath ndara maduong' mawuok Kisumu ka dhi Busia. Namba simu en 22929, 22959, 22983

Janyuol/Jarit	<div>Nyinge</div> <div></div> <div>Nukta ma ochung ne nyinge</div> <div></div>	<div>Sei</div> <div></div> <div>Alama*</div> <div></div>	<div>Tarik</div> <div>/ /</div> <div></div>
<div>Ja ndiko mar IPTi</div> <div><div></div><div></div><div></div></div>	<div>Nyinge</div> <div></div>	<div>Sei</div> <div></div>	<div>Tarik</div> <div>/ /</div> <div></div>
<div>Ja neno*</div>	<div>Nyinge</div> <div></div>	<div>Sei</div> <div></div> <div>Alama**</div> <div></div>	<div>Tarik</div> <div>/ /</div> <div></div>
<div><div>*Janyuol nyalo keto seyi kata keto alama kod janeno bende biro keto seyi mare manyiso ni janyuol/jarit nyathi oyie.</div><div>** Alama miketo gi janyuol kata jarit nyathi en mar lwedo (placing their thumb on an inkpad and pressing down in the space above)</div></div>			

Achiel kuom mama kata baba kata jarit nyathi nyalo keto seyi. Ok dwar seyi mag gi giduto. Janeno dwarore mana kuom joma ok nyal keto seyi.Otas te mar oboke ni nyaka ketie alama mar mama, baba kata jarit nyathi(ng'ano ma oketo seyi e oboke mar Ayie)

IPTi - Malaria Prevention Study

16 - Sick Visit Form

Scanned
& Verified
☐

Registrar code

Interview date (dd/mm/yyyy)

 / /

Health facility

☐ Lwak☐ Abidha☐ Ong'ielo☐ Saradidi

regcode

date_16

hfac_16

IPTi Participant ID number

 -

Record the number from the infant's study ID card. If the guardian has not brought the ID card, please ask them to retrieve the card. If the ID card has been lost, look up the child in the files and create a new ID card.

idnum

Part 1. Study Visit

Which type of study visit is the child here for today?

☐ Unscheduled sick visit**Begin with Part 2.**☐ Scheduled visit when the child was found sick**Begin with Part 3.**

Visit number

visitcode

visitus

Part 2. Location Information

2.01 Child's name

Christian name

Juok name

Father's Juok name

Date of birth (dd/mm/yyyy)

 / /

Child is

☐ Less than 2 months old☐ Equal to or greater than 2 months old

dob

childage

2.02 What is the relationship of the caregiver to the infant?

☐ mother☐ baby sitter☐ other relative☐ unknown☐ father☐ maid (japidi)☐ other not related

caregiver

2.03 Are you (the caregiver) 15 years old or older?

☐ yes ☐ no ☐ unknown

If 'no', Nurse makes assessment whether an older relative should be brought in

cage15

Show the caregiver the village Landmark Code Map in the participant's file.

2.04 Has the infant moved to a new location since the last visit?

☐ yes ☐ no ☐ unknown

If 'yes', record relocation information below and on a new Village Landmark Codemap. If 'no' go to Part 3.

moved

2.04a In which village does infant and caregiver reside?

Name

Number

villname

village

2.04b Have you moved:

☐ new house and new compound in same village☐ new village within clinic catchment☐ new village in catchment of another clinic☐ outside study area**Contact Study Coordinator before continuing**

2.04c What is the name of the current head of compound?

Christian name

wheremov

cfname

Juok name

cjname

Father's Juok name

clname

compound

house

landmark1

landmark2

landmark3

2.04d Compound House:

2.04e Which landmarks does the infant live near?

landmark1

landmark2

landmark3

File/Sick visit number

16-Sick Visit Form

Nurse code

--	--	--

Interview date (dd/mm/yyyy)

		/			/				
--	--	---	--	--	---	--	--	--	--

IPTi Participant ID number

				-		
--	--	--	--	---	--	--

nursecode

date_16_2

Part 3: Treatment History

idnum2

- 3.01 Was the child admitted to a hospital since the last time you visited an IPTi clinic? (since the last time you visited the IPTi study staff in this clinic, or another IPTi study clinic). ☐ yes ☐ no ☐ unknown **If 'no', go to 3.02.**

admitted

- 3.01a Was this admission facilitated by IPTi staff?

☐ yes ☐ no ☐ unknown
If no or unknown, fill Hospital Discharge Form

facilitated

- 3.01b Has your child had a blood transfusion since the last visit?

☐ yes ☐ no ☐ unknown

transfusion_16

- 3.02 Has your child taken any medications in the past 2 weeks **other than those given by study staff?**

☐ yes ☐ no ☐ unknown
If 'no', go to Part 4.

medication

What was your child given?

Show caregiver Medication Reference Sheet and probe for specific medications.

Where was it obtained?

1=this clinic, but not from IPTi staff, 2=other clinic, 3=hospital, 4=duka, 5=other

SP ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

sp
sp_obt

Amodiaquine ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

aq
aq_obt

Septrin (CTX) ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

ctx
ctx_obt

Chloroquine ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

cq
cq_obt

Quinine ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

qu
qu_obt

Co-artem ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

co_artem
co_artem_obt

Cotexin/alaxin ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

cotexin
cotexin_obt

Cosumate ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

cosumate
cosumate_obt

Analgesics ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

anal
anal_obt

Antibiotic ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

antib
antib_obt

Anthelmintic ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

antih
antih_obt

Valium ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

valium
valium_obt

Other: ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

other
other_obt

Medication name

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

treatname

Other: ☐ yes ☐ no ☐ unknown

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

other2
other2

Medication name

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treatname2

File/Sick visit number

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Part 4: Examination

4.01 Vital signs	Pulse	<input type="text"/> <input type="text"/> <input type="text"/>	<i>If > 150 call CO</i>	Respiratory rate	<input type="text"/> <input type="text"/> <input type="text"/>	<i>If >60 call CO</i>	pulse respiration
	Temperature	<input type="text"/> <input type="text"/> <input type="text"/> °C	<i>If T<35.6 or T> 37.4 and <2months, → severe disease If T>39.5 call CO</i>				temp_2
4.02 Is the child able to drink or breastfeed at all?	<input type="radio"/> yes <input type="radio"/> no	→ <i>If 'no', severe disease</i>					breastfeed2
4.03 Does the child vomit everything with each feeding?	<input type="radio"/> yes <input type="radio"/> no	} → <i>If 'yes', severe disease</i>					vomit
4.04 Is the child lethargic or unconscious?	<input type="radio"/> yes <input type="radio"/> no						lethargic
4.05 Is the child convulsing now?	<input type="radio"/> yes <input type="radio"/> no						convulsion
4.06 Does the child have cough or difficult breathing?	<input type="radio"/> yes <input type="radio"/> no	<i>If 'no', go to 4.07.</i>					cough
4.06a How long has the child had the cough?	<input type="text"/> <input type="text"/>	days	<i>If <2months and >59 bpm severe disease</i>				coughdays
4.06b Does the child have fast breathing?	<input type="radio"/> yes <input type="radio"/> no	<i>2-12months and >49 bpm } pneumonia 12-59months and >39 bpm }</i>				breaths	
4.06c Chest indrawing?	<input type="radio"/> yes <input type="radio"/> no	→ <i>If 'yes', severe disease</i>					indrawing
4.06d Nasal flaring?	<input type="radio"/> yes <input type="radio"/> no	→ <i>If 'yes', and <2months, severe disease</i>					flaring
4.06e Stridor when calm?	<input type="radio"/> yes <input type="radio"/> no	→ <i>If 'yes', severe disease</i>					stridor
4.06f Wheezing?	<input type="radio"/> yes <input type="radio"/> no						wheezing
4.07 Does the child have diarrhea?	<input type="radio"/> yes <input type="radio"/> no	<i>If 'no', go to 4.07d</i>					diarrhea
4.07a How long has the child had diarrhea?	<input type="text"/> <input type="text"/>	days					diarrheadays
4.07b Is there blood in the stools?	<input type="radio"/> yes <input type="radio"/> no						stool
4.07c Has the child ever had 2 or more episodes of diarrhea lasting 14 days or more?	<input type="radio"/> yes <input type="radio"/> no						episodes
4.07d Is the child restless or irritable?	<input type="radio"/> yes <input type="radio"/> no						restless
4.07e Does the child have sunken eyes?	<input type="radio"/> yes <input type="radio"/> no						sunkeneyes
4.07f Is the child not able to drink or drinking poorly?	<input type="radio"/> yes <input type="radio"/> no						poordrink
4.07g Is the child drinking eagerly, thirsty?	<input type="radio"/> yes <input type="radio"/> no						thirsty
4.07h After pinching the skin does it go back?	<input type="radio"/> very slowly <input type="radio"/> slowly <input type="radio"/> normally						pinch

* If 2 of: lethargic, unconscious, sunken eyes, drink poorly, or skin pinch very slowly → severe disease

File/Sick visit number

- 4.08 Does the child have measles now, or in the past 3 months? ☐ yes ☐ no measles3mon
- 4.09 Does the child have a stiff neck? ☐ yes ☐ no → *If 'yes', severe disease* stiffneck
- 4.10 Does the child have bulging fontanelle? ☐ yes ☐ no → *If 'yes', severe disease* fontonelle
- 4.11 Does the child have a runny nose? ☐ yes ☐ no runnynose
- 4.12 Does the child have a rash? ☐ yes ☐ no rash
If 'no', go to 4.13
- 4.12a Is it a localized heat or diaper rash? ☐ yes ☐ no diaperrash
If 'no', fill the Skin Reaction Form
- 4.13 Does the child have red eyes? ☐ yes ☐ no reeyes
- 4.14 Does the child have mouth ulcers? ☐ yes ☐ no (If 'no', go to 4.15) mouthulcers
If 'yes', fill the Skin Reaction Form
- 4.14a Are they deep and extensive? ☐ yes ☐ no → *If 'yes', severe disease* deepulcers
- 4.15 Does the child have pus draining from the eye(s)? ☐ yes ☐ no → *If 'yes' and <2months, severe disease* puseyes
- 4.16 Is there clouding of the cornea? ☐ yes ☐ no → *If 'yes' and measles, severe disease* clouding
- 4.17 Does the child have an ear problem? ☐ yes ☐ no earproblem
If 'no', go to 4.18.
- 4.17a Is there pus draining from the ear? ☐ yes ☐ no → *If 'yes' and <2months severe disease* pusear
- 4.17b Is there tender swelling behind the ear? ☐ yes ☐ no → *If 'yes', severe disease* tenderswell
- 4.18 Is there visible severe wasting? ☐ yes ☐ no → *If 'yes', severe disease* wasting
- 4.19 Is there oedema of both feet? ☐ yes ☐ no → *If 'yes', severe disease* oedema
- 4.20 Weight for age: ☐ very low ☐ not very low weight
- 4.21 Is the growth faltering?(weight curve flattening or dropping for at least 2 consecutive months) ☐ yes ☐ no faltering
- 4.22 Is the child jaundiced? ☐ yes ☐ no jaundice
- 4.23 Are there enlarged lymph nodes at 2 or 3 of the following sites (neck, axillae, groins) ☐ yes ☐ no lymphnodes
- 4.24 Oral thrush? ☐ yes ☐ no oralthrush
- 4.25 Any signs of anemia
- 4.25a Palmar pallor? ☐ yes ☐ no palmarp
- 4.25b Nail bed pallor? ☐ yes ☐ no nailp
- 4.25c Conjunctiva/lip/tongue pallor? ☐ yes ☐ no otherp
- 4.26 Has the child had hot body in the last 48 hours or is the temperature >37.4 now? ☐ yes ☐ no hotbody

✱ **Note: If child has severe disease, give urgent pre-referral treatment, refer the child and notify Clinic Officer**

File/Sick visit number

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Part 5: Samples

IF hot body in last 48 hours OR temp >37.4 OR signs of anemia do Haemoglobin, OptiMal, and Blood Slide.

HAEMOGLOBIN TEST

5.01 Hemoglobin

g/dl

**If visit 6, 7, 8 copy onto
Scheduled Visit Form part 11**

*** IF <5.6 g/dl call CO,**

*** IF <5.1 g/dl, Refer, call CO**

*** IF <8.0 g/dl, Give Treatment Iron**

PERFORM OPTIMAL TEST

5.02 OptiMal result

☐ positive ☐ negative

**If 'positive', note on Study
ID card and give to
Pharmacy Technician**

MAKE BLOOD SLIDE

5.03 Blood slide done

☐ yes ☐ no

**If visit 6, 7, 8 copy onto
Scheduled Visit Form part 11**

hb_16

optimal_16

bloodslide

If visit 2, 4, 5 or 6 go to part 11 of Scheduled Visit Form and collect appropriate blood sample.

Part 6: Diagnosis If child is < 2months old, refer to IMCI guidelines to make diagnosis

6.01 What do you diagnose the child with?

Malaria

☐ yes

Meningitis

☐ yes

svmalaria
svmeningitis

Severe malaria

☐ yes

Otitis media

☐ yes

svs malaria
svotitis

Pneumonia

☐ yes

Conjunctivitis

☐ yes

svpneumonia
svconjunctiva

Severe pneumonia

☐ yes

Gastroenteritis

☐ yes

svspneumonia
svgastroent

Upper Respiratory Tract Infection(URTI)

☐ yes

Diarrhoea

☐ yes

svurti
svdiarrhoea3
svbronchospasm
svdehydration

Wheezing/bronchospasm

☐ yes

Dehydration

☐ yes

Anemia

☐ yes

Dysentery

☐ yes

svanemia
svdysentery

Severe anemia

☐ yes

Ring worm

☐ yes

svsanemia
svringworm

Malnutrition

☐ yes

Intestinal worms

☐ yes

svmalnutrition
svworms

Severe malnutrition

☐ yes

Wound

☐ yes

svsmalnutrition
svwound

Measles

☐ yes

Septic wound/ulcers

☐ yes

svmeasles
svulcers

Oral candidiasis

☐ yes

Burn

☐ yes

svcandidiasis
svburn

Scabies

☐ yes

Diaper rash

☐ yes

svscabies
svdiaperrash

Rash

☐ yes

Heat rash

☐ yes

svrashd
svheatrash
svfever39_5

Fever >39.5, no other signs of illness

☐ yes

Other1

☐ yes

svotherd1
svothercode1

Other2

☐ yes

svotherd2
svothercode2

6.02 If there is any error in part 6.01, shade these two circles ☐ yes ☐ yes

anyerror

Part 7: Medication

7.01 Did you or will you give antimalarial treatment

☐ yes ☐ no

If 'no', go to 7.02.

antimalaria_16

7.01a What was given?

☐ Quinine sulfate

☐ Special antimalarial treatment per protocol

☐ co-artem

specialantimal

☐ Other

othername

File/Sick visit number

Refer to 4.02: OptiMal results. If result is positive, Pharmacy Technician is preparing treatment. Administer treatment once ready.

7.02 What other medications were given today?

Albendazol syrup	<input type="radio"/> yes	Sallbutamol/ventolin	<input type="radio"/> yes	malbendaz
Amoxicilline syrup	<input type="radio"/> yes	Benzyl benzoate emulsion	<input type="radio"/> yes	msalbutamol
Benzoic /slicyl acid ointment	<input type="radio"/> yes	Ceftriaxone injection	<input type="radio"/> yes	mamoxicil
Clotrimazole cream	<input type="radio"/> yes	Clotrimazole oral paint	<input type="radio"/> yes	mbenzyl
Cloxacillin syrup	<input type="radio"/> yes	Piriton/chlorophenilamine	<input type="radio"/> yes	mbenzoic
Erythromycin syrup	<input type="radio"/> yes	Ferrous sulphate(vit B complex)	<input type="radio"/> yes	mceftriax
Gentamycin eye drops	<input type="radio"/> yes	Gentian violet crystals	<input type="radio"/> yes	mclotcream
Metronidazole suspension	<input type="radio"/> yes	Multivitamin syrup	<input type="radio"/> yes	mclotpaint
Oral rehydration salts	<input type="radio"/> yes	Paracetamol	<input type="radio"/> yes	mcloxacill
Praziquantel (biltricide)	<input type="radio"/> yes	Quinine injection	<input type="radio"/> yes	mpiriton
Sulphadiazine cream	<input type="radio"/> yes	Tetracycline eye ointment	<input type="radio"/> yes	merythrom
Vitamin A	<input type="radio"/> yes	Valium injection	<input type="radio"/> yes	mferrous
Valium tablets	<input type="radio"/> yes	Hydrocortisone cream	<input type="radio"/> yes	mgentamycin
Cough expectorant	<input type="radio"/> yes	Chloramphenicol IM	<input type="radio"/> yes	mgentian
				mmetronidaz
				mmultivit
				mors
				mparacetam
				mpraziquant
				mquinjection
				mtetracyc
				msulphadiaz
				mvitamia
				mvaliuminj
				mvaliumtab
				mhydrocort
				mcoughexpect
				mchloramphim
Other 1	<input type="radio"/> yes			mother1
Other 2	<input type="radio"/> yes			mothername1
				mother2
				mothername2

7.02a If there is any error in part 7.02, shade these two circles ☐ yes ☐ yes anyerror2

Part 8: Disposition

8.01 Based on IMCI classification the child has?

☐ mild disease

☐ moderate disease

☐ severe disease

→ Give pre-referral treatment , refer the child and call CO

8.02 What is the disposition of the child ?

☐ home ☐ PGH

☐ Lwak ☐ other

disposition

otherdisp

* If hospitalized for observation or treatment notify CO. All children being referred must be sent with a referral form. If child is being referred to hospital, do not give intervention drug

Return to part 6 of Scheduled Visit Form if child is present for a Scheduled visit. If child is referred to a hospital, do not give intervention drug.

Part 9: Adverse Event Classification

Clinical Officer code

cliniccode

9.01 Is Grade 3 AE or SAE suspected ?

☐ yes ☐ no

If 'yes', fill AE Investigation form

SAE

SVAEnumber

Write AE Form file number here

File/Sick visit number

IPTi - Malaria Prevention Study
17 - Immunization Schedule Form

Participant ID Number

 -

idnum
hfac_17

Immunization

Date(dd/mm/yyyy)

BCG	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	bcg bcgdate
OPV 0	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	opv0 opv0date
OPV 1	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	opv1 opv1date
PENT 1	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	pent1 pent1date
OPV 2	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	opv2 opv2date
PENT 2	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	pent2 pent2date
OPV 3	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	opv3 opv3date
PENT 3	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	pent3 pent3date
Measles	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	measles measdate
Vitamin A : Dose 1	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	vitamina1 vitamina1date
Vitamin A : Dose 2	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	vitamina2 vitamina2date
Vitamin A : Dose 3	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	vitamina3 vitamina3date
Vitamin A : Dose 4	<input type="radio"/> given <input type="radio"/> missed	<div><div></div><div></div></div> / <div><div></div><div></div></div> / <div><div></div><div></div><div></div><div></div></div>	vitamina4 vitamina4date

Date form completed (dd/mm/yyyy)

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/

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date_17

Notes:

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IPTi - Malaria Prevention Study
19 - Hospital Discharge Form

Staff code

IPTi Participant ID number

-

Date (dd/mm/yyyy)

/

/

AE number

staffcode

idnum

date_19

aenumber_19

Copy from the AE Investigation Form Filing Number

Part 1. Identifying Information

1.01 Child's name

Christian name

Juok name

Father's Juok name

1.02 Child's date of birth

dd/mm/yyyy

/

/

hddob_19

File/Discharge number

19- Hospital Discharge Form

IPTi Participant ID number

					-		
--	--	--	--	--	---	--	--

AE number

--	--	--	--	--

**Copy from the AE
Investigation Form
Filing Number**

Date(dd/mm/yyyy)

		/			/				
--	--	---	--	--	---	--	--	--	--

date_19_2
aenumber_19_2

Part 2: Discharge

2.01 Date admitted

		/			/				
--	--	---	--	--	---	--	--	--	--

idnum2

hdadmdate

hdhospital

2.02 Hospital

☐ Lwak ☐ Bondo ☐ NGPH

☐ other _____

hdhospother

2.02a If admitted to NPGH, Write hospital number here
(Found on outside cover of hospital chart)

					-		
--	--	--	--	--	---	--	--

hdipnum

2.03 Did the child receive blood transfusion during admission?

☐ yes ☐ no

hdtransfusion

2.03a If yes, date of transfusion

		/			/				
--	--	---	--	--	---	--	--	--	--

hdtransdate

2.04 Was a malaria blood slide done during the hospital admission?

☐ yes ☐ no

hdbsdone

2.04a If yes, date of slide

		/			/				
--	--	---	--	--	---	--	--	--	--

hdbsdate

2.04b If yes, where was the slide done?

☐ Walter Reed ☐ Main Hospital Laboratory

hdbslab

☐ CRC lab

☐ Other _____

hdbslabother

2.04c If slide was made, what was the result?

☐ Positive ☐ Negative

hdbsresult

☐ Indeterminate ☐ Unknown

2.04d If blood slide was positive, what was the species?

☐ P falciparum

☐ P falciparum gametocyte only

hdpfalciparum
hdpfalciparumgarr
hdpmalariae
hdpfmmixed
hdspcother
hdspcothername

☐ P malariae

☐ Mixed infection P falciparum+P malariae

☐ Other _____

2.04e If yes, what was the disposition of the slide?

☐ CRC-lab ☐ Sent to Kisian for re-reading

hdbsdisposition

☐ Discarded ☐ unknown

2.05 Was a complete hemogram done during this admission?

☐ yes ☐ no

hdhgdone

2.05a If yes, where was the test performed?

☐ Walter Reed ☐ Main Hospital Laboratory

hdhglab

☐ CRC lab

☐ Other _____

hdhglabother

File/Discharge number

--	--	--	--	--

2.05b If yes, record results below

NOTE: If more than one hemogram done during admission, record one with the lowest hemoglobin value.

WBC	<input type="text"/> <input type="text"/> <input type="text"/>	X10 ³ /uL	hdwb
RBC	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	X10 ⁶ /uL	hdrrbc
Hgb	<input type="text"/> <input type="text"/> <input type="text"/>	g/dL	hdhb
Hct	<input type="text"/> <input type="text"/> <input type="text"/>	%	hdhct
MCV	<input type="text"/> <input type="text"/> <input type="text"/>	fL	hdmc
MCH	<input type="text"/> <input type="text"/> <input type="text"/>	pg	hdmc
MCHC	<input type="text"/> <input type="text"/> <input type="text"/>	g/dL	hdmc
Plt	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	X10 ⁹ /L	hdplt
LY%	<input type="text"/> <input type="text"/> <input type="text"/>	%	hdly_percent
LY #	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	X10 ³ /uL	hdly_

2.06 Was a hemocue measurement done during admission? ☐ yes ☐ no ☐ unknown

hdhqdone

2.06a If yes, record the value

hdhq

NOTE: If more than one hemocue measurement was taken during admission, record one with the lowest hemoglobin value.

2.07a Did the child have a measured axillary temperature of > 37.4 during this hospital admission? ☐ yes ☐ no ☐ unknown

hdaxiltemp

2.07b Did the child have prostration? ☐ yes ☐ no ☐ unknown

hdprostate

2.07c Did the child have impaired consciousness? ☐ yes ☐ no ☐ unknown

hdconscious

2.07d Did the child have respiratory distress or acidotic breathing? ☐ yes ☐ no ☐ unknown

hdldistress

2.07e Did the child have 2 or more convulsions? ☐ yes ☐ no ☐ unknown

hd2convulse

2.07f Did the child have circulatory collapse? ☐ yes ☐ no ☐ unknown

hdcollapse

2.07g Did the child have radiographically confirmed pulmonary oedema? ☐ yes ☐ no ☐ unknown

hdpoedema

2.07h Did the child have abnormal bleeding? ☐ yes ☐ no ☐ unknown

hdableeding

2.07i Did the child have jaundice? ☐ yes ☐ no ☐ unknown

hdjaundice

2.07j Did the child have haemoglobinuria? ☐ yes ☐ no ☐ unknown

hdhglobinura

2.07k Did the child have hypoglycemia? ☐ yes ☐ no ☐ unknown

hdglycemia

2.07l Was blood glucose measured? ☐ yes ☐ no ☐ unknown

hdglucose

Write down the amount of glucose in blood

mmol/L

hdglucosevm

File/Discharge number

2.08 Did the child receive antimalarial treatment during admission? ☐ yes ☐ no ☐ unknown

hdantimalarial_15

2.08a If yes, What date was antimalarial treatment begun?
(If more than one antimalarial given record date
first antimalarial given)

 / /

hddateantimal

2.08b If yes, fill in circle for each antimalarial that
was given

☐ SP / Fansidar / Metakelfin ☐ Amodiaquine ☐ Cosumate

☐ Quinine Injection ☐ Cotexin/Alaxin ☐ Co-artem

☐ Quinine tablets ☐ Malarone ☐ unknown

☐ other

hdsp
hdamodiaquine
hdcosumate
hdquinineinj
hdcotexin
hdcoartem
hdquininetab
hdmalarone
hdnotknown
hdothermaldrug
hdothdrugname
hdanyerror

2.08c If there is any error in part 2.08b, shade these two circles ☐ yes ☐ yes

2.09 Did the child receive any sulfa-containing antibiotics
during admission (septrin/cotrimoxazole) ☐ yes ☐ no ☐ unknown

hdsulfantibiotic

2.10 Did the child receive any antimalarials to take at home upon
discharge? ☐ yes ☐ no ☐ unknown

hdantimalhome

2.10a If yes, what antimalarials were given on discharge? (Shade all that apply)

Medication**No days****How Dispensed**

(1=Pills given 2=Prescription Written 3=Other)

☐ SP/ Fansidar / Metakelfin

☐ 1 ☐ 2 ☐ 3

☐ Amodiaquine

☐ 1 ☐ 2 ☐ 3

☐ Quinine tablets

☐ 1 ☐ 2 ☐ 3

☐ Cosumate

☐ 1 ☐ 2 ☐ 3

☐ Cotexin/Alaxin

☐ 1 ☐ 2 ☐ 3

☐ Co-artem

☐ 1 ☐ 2 ☐ 3

☐ Malarone

☐ 1 ☐ 2 ☐ 3

☐ other

☐ 1 ☐ 2 ☐ 3

hdsp
hdsp_day
hdsp_disp
hdaqh
hdaq_day
hdaq_disp
hdquh
hdqu_day
hdqu_disp
hdcosh
hdcos_day
hdcos_disp
hdcot
hdcot_day
hdcot_disp
hdcoarth
hdcoart_day
hdcoart_disp
hdmalh
hdmal_day
hdmal_disp
hdothh
hddrgna
hdoth_day
hdoth_disp
hdanyerror3

2.10b If there is any error in part 2.10a, shade these two circles ☐ yes ☐ yes

File/Discharge number

2.11 Did the child receive any sulfa-containing antibiotics to take at home upon discharge (septrin/cotrimoxazole)?

☐ yes ☐ no ☐ unknown

hdsulfantibh

2.11a If yes, what antibiotics were given on discharge? (Shade all that apply)

Medication (If recommended to take medication indefinitely code number of days as 99)	No days	How Dispensed (1=Pills given 2=Prescription Written 3=Other)	
<input type="radio"/> Septrin/cotrimoxazole	<div><div></div><div></div></div>	<input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3	hdseph hdsep_day hdsep_disp
<input type="radio"/> Other	<div><div></div><div></div></div>	<input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3	hdothph hdothp_day hdothp_disp

2.11b If there is any error in part 2.11a, shade these two circles

☐ yes ☐ yes

hdanyerror4

2.12 What were the hospital discharge diagnoses?
(These may be different from the CO judgement of AE diagnoses on forms 29&30)

Malaria	<input type="radio"/> yes	Meningitis	<input type="radio"/> yes	hdmalaria hdmeningitis
Severe malaria	<input type="radio"/> yes	Otitis media	<input type="radio"/> yes	hds malaria hdotitis
Pneumonia	<input type="radio"/> yes	Conjunctivitis	<input type="radio"/> yes	hdpneumonia hdconjunctiva
Severe pneumonia	<input type="radio"/> yes	Gastroenteritis	<input type="radio"/> yes	hds pneumonia hdgastroent
Upper Respiratory Tract Infection(URTI)	<input type="radio"/> yes	Diarrhoea	<input type="radio"/> yes	hdurti hddiarrhoea3
Wheezing/bronchospasm	<input type="radio"/> yes	Dehydration	<input type="radio"/> yes	hdbronchospasm hddehydration
Anemia	<input type="radio"/> yes	Dysentery	<input type="radio"/> yes	hdanemia hddysentery
Severe anemia	<input type="radio"/> yes	Intestinal worms	<input type="radio"/> yes	hds anemia hdworms
Malnutrition	<input type="radio"/> yes	Wound	<input type="radio"/> yes	hdmalnutrition hdwound
Severe malnutrition	<input type="radio"/> yes	Septic wound/ulcers	<input type="radio"/> yes	hds malnutrition hdulcers
Measles	<input type="radio"/> yes	Burn	<input type="radio"/> yes	hdmeasles hdburn
Oral candidiasis	<input type="radio"/> yes	Rash	<input type="radio"/> yes	hdcandidiasis hdrashd
Scabies	<input type="radio"/> yes			hdsabies
Other1	<input type="radio"/> yes			hdotherd1 hdothrcode1
Other2	<input type="radio"/> yes			hdotherd2 hdothrcode2

2.12a If there is any error in part 2.12, shade these two circles

☐ yes ☐ yes

hdanyerror2

2.13 Outcome

☐ alive ☐ absconded
☐ dead ☐ transferred

hdoutcome

2.14 Date of discharge/death/absconding (dd/mm/yyyy)

/ /

hddischarge date

File/Discharge number

Interview date

--	--	--	--	--	--	--	--

Note: Clinical Officer or designated medical staff should fill this form for all clinical AEs.

Part 1: Identifying information

1.01 Infant's name

Christian name

[illegible]

Juok name

[illegible]

Father's Juok name

[illegible]

1.02 Infant's date of birth

(dd/mm/yyyy)

$$\boxed{} \boxed{} / \boxed{} \boxed{} / \boxed{} \boxed{} \boxed{} \boxed{}$$

1.03 Infant's gender ☐ Male ☐ Female

1.04 Infant's date of enrollment

(dd/mm/yyyy)

--	--

 /

--	--

 /

--	--	--	--

name

dob

mname
sex

Iname

enrolldate

idnum

File / AE number

--	--	--	--	--

29 - Adverse Events Investigation Form

Clinic Officer code

IPTi Participant ID number

-

Interview date (dd/mm/yyyy)

/

/

idnum2

cliniccode2

date_29_2

Was this AE preceded by a sick visit?

yes No

AEIpreceed

If yes, write Sick Visit Form filing number here

AEIfilenum

Part 2: Investigation

2.01 Notification of Adverse Event was received from whom?

IPTi Nurse

IPTi coordinator

Non IPTi clinic staff

DSS staff

PGH staff

IPTi clinical officer

Other

AEIsource

AEIothersource

2.02 Onset date

/

/

AEIdateonset

2.03 Date of awareness by IPTi staff

/

/

AEIawaredate

2.04 AE diagnosis name(s)

(check all that apply)

Malaria

yes

Meningitis

yes

aeimalaria

aeimeningitis

Severe malaria

yes

Jaundice

yes

aeismalaria

aeijaundice

Pneumonia

yes

Conjunctivitis

yes

aeipneumonia

aeiconjunctiva

Severe pneumonia

yes

Gastroenteritis

yes

aeispneumonia

aeigastroent

Wheezing/bronchospasm

yes

Diarrhoea

yes

aeibronchospasm

aeidiarrhoea3

Anaphylaxis

yes

Dehydration

yes

aeianaphylaxis

aeidehydration

Stevens Johnson syndrom/TEN

yes

Dysentery

yes

aeisten

aeidysentery

Drug rash

yes

Neutropenia

yes

aeidrashd

aeineutropenia

Anemia

yes

Stomatitis/oral ulcers

yes

aeianemia

aeistomatitis

Severe anemia

yes

Temperature >39.5

yes

aeisanemia

aeitemp_39_5

Malnutrition

yes

Septic wound/ulcers

yes

aeimalnutrit

aeiulcers

Measles

yes

Burn

yes

aeimeasles

aeiburn

Fever >39.5, no other signs of illness

yes

aeifever39_5

Other

Code

aeiname

aeiotherd1

aeiothercode1

Other

Code

aeiname2

aeiotherd2

aeiothercode2

2.04a If there is any error in part 2.04, shade these two circles

yes yes

AEIanyerror

File / AE number

IPTi - 29-Adverse Events Investigation Form - FINAL-Version 2.5

Page 2 of 6

2.05 Was client hospitalized? ☐ yes ☐ no

AEIhospitalized

2.06 Dates 1st dose of study drug was given

/

/

to

/

/

☐ study drug not yet administered

AEIdosedate1
AEIdosedate1b
AEIsdruggiven1

2.07 Dates 2nd dose of study drug was given

/

/

to

/

/

☐ study drug not yet administered

AEIdosedate2
AEIdosedate2b
AEIsdruggiven2

2.08 Dates 3rd dose of study drug was given

/

/

to

/

/

☐ study drug not yet administered

AEIdosedate3
AEIdosedate3b
AEIsdruggiven3

2.09 Does the participant need to be withdrawn from the study?

☐ yes ☐ no ☐ already withdrawn ☐ N/A

AEIwithdrawism

2.10 At the time of completing this report, determine status of adverse event

☐ Resolved ☐ Not resolved ☐ N/A
Go to 2.12

AEIresolved

2.11 If event is resolved determine outcome **Go to 2.13**

☐ Died, participant history and cause known ☐ Event resolved with disability
☐ Event resolved without disability ☐ N/A
☐ Other

AEIstatus1
AEIotherstatus1

2.12 If event is not resolved, determine status

☐ Participant hospitalized ☐ Participant home: event ongoing ☐ N/A
☐ Participant in clinic: event ongoing ☐ Participant died, history or cause not known
☐ Other

AEIstatus2
AEIotherstatus2

If event is not resolved, continue to follow participant, fill AE Update Form when necessary and until AE is resolved

2.13 Narrative of event:

Include history of present illness, symptoms, other medication usage, other medical history, pertinent physical findings, laboratory/X-ray diagnosis, treatment of adverse event, and follow up required. Also include any protocol violations or erroneous drug administration that may have contributed to the event.

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File / AE number

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Part 3: Categorization/Reporting: (TO BE COMPLETED BY THE PRINCIPAL INVESTIGATOR)

Investigator code

7

AEIPIcode

3.01 DSMB

Categorization of Event

Reporting Timeline

AEIdsmgrade

- ☐ SAE - death
- Within 7 days of event
- ☐ SAE - hospitalization for unexpected or unusual cause,
including critical anemia(hb<5.0) OR
related to study drug
- Within 7 days of event
- ☐ SAE - hospitalization for common childhood illness
- Quarterly report
- ☐ SAE - Life threatening event, not hospitalized
- Within 7 days of event
- ☐ SAE - Event resulting in disability, not hospitalized
- Within 7 days of event
- ☐ AE - Grade 3 AND related to study drug
- Within 7 days of event
- ☐ AE - Grade 3 AND NOT related to study drug, No hospitalization,
OR refused hospitalization
- Not reported
- ☐ Grade 1 or 2AE, or not an AE or SAE
- Not reported

3.02 CDC/KEMRI IRB/ERC

Cartegorization of Event

Reporting Timeline

AEIcdgrade

- ☐ SUAEP- Serious unexpected event resulting in death or
hospitalization, AND at least possibly related to study drug
- Informal E-mail within 2 working days
Formal report within 7 days of event
- ☐ AAE- Deaths or hospitalizations from common
childhood illness
- Yearly renewal report
- ☐ Not an AAE, or SUAEP
- Not reported

3.03 Determine the causal relationship to investigation drug administration

- ☐ definite (most probable)
- ☐ probable
- ☐ possible
- ☐ unlikely
- ☐ not related
- ☐ unclassified
- AEIprobable

3.04 Should the participant be withdrawn from the study?

- ☐ yes
- ☐ no
- ☐ already withdrawn
- ☐ died
- AEIwithdrawpi

3.05 Signature of investigator

sign

3.06 Date of signature

/

/

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AEIsigndate

File / AE number

IPTi - Malaria Prevention Study
30 - Adverse Events Update Form

AE number

Clinical officer code

IPTi Participant ID number

Interview date (dd/mm/yyyy)

staffcode
AENumber
idnum
date_30
cliniccode

Note: Clinical Officer or designated medical staff should fill this form for all unresolved AEs.

Part 1: Identifying information

1.01 Infant's name

Christian name

Juok name

Father's Juok name

1.02 Infant's date of birth

(dd/mm/yyyy)

name
dob
mname
sex
lname
enrolldate
idnum

1.03 Infant's gender ☐ Male ☐ Female

1.04 Infant's date of enrollment

(dd/mm/yyyy)

30- Adverse Events Update Form

AE number

Clinical officer code

IPTi Participant ID number

-

Interview date (dd/mm/yyyy)

AENumber2

idnum2

date_30_2

cliniccode2

Part 2: Update on Event

2.01 Has the event:

☐ increased in severity

☐ decreased in severity

☐ no improvement

AEUseverity

2.02 AE diagnosis name(s) *Final AE diagnoses should be assigned based on CO judgement rather than hospital discharge diagnoses.*

Malaria	<input type="radio"/> yes	Meningitis	<input type="radio"/> yes	aeumalaria aeumeningitis
Severe malaria	<input type="radio"/> yes	Jaundice	<input type="radio"/> yes	aeusmalaria aeujaundice
Pneumonia	<input type="radio"/> yes	Conjunctivitis	<input type="radio"/> yes	aeupneumonia aeuconjunctiva
Severe pneumonia	<input type="radio"/> yes	Gastroenteritis	<input type="radio"/> yes	aeuspneumonia aegastroent
Wheezing/bronchospasm	<input type="radio"/> yes	Diarrhoea	<input type="radio"/> yes	aeubronchospasm aediarrhoea3
Anaphylaxis	<input type="radio"/> yes	Dehydration	<input type="radio"/> yes	aeuanaphylaxis aedehydration
Stevens Johnson syndrom/TEN	<input type="radio"/> yes	Dysentery	<input type="radio"/> yes	aeusten aeadysentery
Drug rash	<input type="radio"/> yes	Neutropenia	<input type="radio"/> yes	aeudrashd aeuneutropenia
Anemia	<input type="radio"/> yes	Stomatitis/oral ulcers	<input type="radio"/> yes	aeuanemia aestomatitis
Severe anemia	<input type="radio"/> yes	Temperature >39.5	<input type="radio"/> yes	aeusanemia aeutemp_39_5
Malnutrition	<input type="radio"/> yes	Septic wound/ulcers	<input type="radio"/> yes	aeumalnutrition aeuulcers
Measles	<input type="radio"/> yes	Burn	<input type="radio"/> yes	aeumeasles aeburn
Fever >39.5, no other signs of illness	<input type="radio"/> yes			aeufever39_5

☐ Other

Code

aeuname
aeuotherd1
aeuothercode1

☐ Other

Code

aeuname2
aeuotherd2
aeuothercode2
aeuanyerror

2.02a If there is any error in part 2.02, shade these two circles ☐ yes ☐ yes

2.03 Date that most recent dose of study drug was given

/

/

to

/

/

☐ study drug not yet administered

AEUdosedate1
AEUdosedate1b
AEUdruggiven1

AEUwithdrawlsm

AEUresolved

AEUstatus1

AEUotherstatus1

AEUstatus2

AEUotherstatus

If event is not resolved, continue to follow participant, fill AE Update Form when necessary and until AE is resolved

2.08 Describe update on the event

This image shows a single sheet of white paper with horizontal ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

Filenum/Pagelink

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Part 3: Categorization/Reporting: (TO BE COMPLETED BY THE PRINCIPAL INVESTIGATOR)

Investigator Code

7

AEUPIcode

3.01 DSMB

Final Categorization of Event

Reporting Timeline

AEUdsmgrade

- ☐ SAE - death
- Within 7 days of event
- ☐ SAE - hospitalization for unexpected or unusual cause,
including critical anemia(hb<5.0) OR
related to study drug
- Within 7 days of event
- ☐ SAE - hospitalization for common childhood illness
- Quarterly report
- ☐ SAE - Life threatening event, not hospitalized
- Within 7 days of event
- ☐ SAE - Event resulting in disability, not hospitalized
- Within 7 days of event
- ☐ AE - Grade 3 AND related to study drug
- Within 7 days of event
- ☐ AE - Grade 3 AND NOT related to study drug, No hospitalization,
OR refused hospitalization
- Not reported
- ☐ Grade 1 or 2AE, or not an AE or SAE
- Not reported

3.02 CDC/KEMRI IRB/ERC

Final Cartegorization of Event

Reporting Timeline

AEUcdcgrade

- ☐ SUAEP- Serious unexpected event resulting in death or
hospitalization, AND at least possibly related to study drug
- Informal E-mail within 2 working days
Formal report within 7 days of event
- ☐ AAE- Deaths or hospitalizations from common
childhood illness
- Yearly renewal report
- ☐ Not an AAE, or SUAEP
- Not reported

3.03 Has the determination of causal relationship changed since AE Investigation form was completed?

- ☐ yes ☐ no

AEUcausecha

3.03a If yes, record new proposed causal relationship

- ☐ definite (most probable) ☐ probable ☐ possible ☐ unlikely ☐ not related ☐ unclassified

AEUprobable

3.04 Should the participant be withdrawn from the study?

- ☐ yes ☐ no ☐ already withdrawn ☐ Died

AEUwithdrawpi

3.05 Signature of investigator

sign

3.06 Date of signature

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AEUsigndate

Filenum/Pagelink

IPTi -

Malaria Prevention Study

36 - STUDY Form

Health Facility: _____

Head of compound's name
Christian name

Juok name

Father's Juok name

Infant's name
Christian name

Juok name

Father's Juok name

Mother / Father / Guardian's name
Christian name

Juok name

Father's Juok name

Village

DSS Permanent ID

DSS Permanent ID

	Date seen	Date of next visit	OptiMal + / - /ND	Study Drug Given Day 1	Day 2	Day 3
Visit 1 Enrollment	_____	_____	<div><div></div></div>			
Visit 2 Pent 2 (IPTi1)	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>
Visit 3 Pent 3 (IPTi2)	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>
Visit 4 18 weeks	_____	_____	<div><div></div></div>			
Iron Visit	_____	_____				
Visit 5 Measles (IPTi3)	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>
Visit 6 12 months	_____	_____	<div><div></div></div>			
Visit 7 18 months	_____	_____	<div><div></div></div>			
Visit 8 24 months	_____	_____	<div><div></div></div>			
Missed medication	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>
Missed medication	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>
Missed medication	_____	_____	<div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>	<div><div></div><div></div><div></div></div>

Infant's date of birth (dd/mm/yyyy) / /

IPTi - Malaria Prevention Study
41-G6PD Results Form

Laboratory Filing Number

(labfilenum)

Date (dd/mm/yyyy)

(date_41)

IPTi ID number	Blood sample Number	Gender	Genotype	Phenotype
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(idnum)

(Bsnnum)

(Gend)

(Genotype)

(Phenotype)

Laboratory Staff code

(labcode)

Filenum_41

IPTi - Malaria Prevention Study 41-G6PD Results Form

IPTi ID number	Blood sample Number	Gender	Genotype	Phenotype
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